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ORIGINAL ARTICLES

STUDIES ON THE PREVENTION OF MUMPS

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THE development of satisfactory procedures for the propagation of mumps virus in the chick embryo has brought within reach the possibility of immunization against the disease. Before discussing the various approaches to prevention of mumps, it is well to define clearly the need for such vaccines and who should be vaccinated.

Mumps on the whole is a childhood disease and usually mild when restricted to the salivary glands. In the adult the disease may be more severe, particularly on account of so-called complications such as the involvement of the reproductive glands in the male. In view of this experience vaccination of children should be attempted only if (a) a prolonged immunity can be attained or (b) if certain other clinical conditions in the child render an attack of mumps undesirable at a particular time. In the latter case as well as in adults vaccination may be considered of value even if only a short term immunity can be induced. Vaccines appear desirable for susceptible parents, for instance, who have been exposed by their children, for hospital staffs in contact with mumps patients, and for college students or military personnel, where outbreaks of the disease may interrupt the normal course of training.

A second point to be considered concerns the question of susceptibility. It has been well established, particularly since the advent of specific immunologic procedures, that mumps virus causes overt disease in about two thirds of human beings; in the other third the infection remains inapparent but nevertheless induces permanent immunity. Thus it is obvious that not everybody without a history of clinical mumps is susceptible and should be considered eligible for vaccination. Through the studies of Enders and his coworkers it is pos-

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This presentation has been abstracted from more detailed papers to be published elsewhere in collaboration with Drs. Joseph Stokes, Jr., Jane S. and Carrol F. Burgoon and Winslow J. Bashe, Jr. The work summarized was conducted under the Commission on Immunization, Armed Forces Epidemiological Board, Preventive Medicine Service, Office of the Surgeon General, United States Army.

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sible now to determine susceptibility to mumps with a fair degree of accuracy by either skin tests, or complement-fixation reactions. The former appears to be more reliable in the adults, the latter more accurate in children. The experience gained with these tests in our laboratory indicate that, on the whole, either one of the tests permits a fairly accurate prediction of the immune status of an individual. However, exceptions were noted in that a few cases of mumps occurred in subjects which were judged immune by either one of the tests and, conversely, an individual negative in one of the reactions is not necessarily susceptible.

These findings have been put to practical use in a few instances where mumps occurred on hospital wards in patients a few days after admission. Patients and personnel judged susceptible by the two tests were isolated or restricted in their activity and secondary cases occurred only among these. Thus the tests for susceptibility permitted the proper handling of the situation without unnecessary interruption of the therapeutic regimen of individual patients and no further cases complicated the hospital ward routine.

In the studies on immunization against mumps only individuals who were judged susceptible by history and by complement-fixation tests were included. These experiments were conducted to a large extent in southeastern Alaska where major mumps epidemics had been absent for over eight years, thus insuring a large number of susceptible individuals. Three types of immunization procedures were explored: (1) intradermal vaccination with inactivated virus (i.e., skin test); (2) subcutaneous vaccination with inactivated virus concentrated from allantoic fluid prepared according to the principles of influenza vaccine production; (3) oral spraying of attenuated active virus. Whereas inactive virus vaccines, as a rule, will produce only transitory resistance, the attenuated active virus conceivably may result in prolonged immunity in analogy to the natural infection. None of these studies has advanced far enough as yet to permit a final evaluation and the data to be presented should be taken merely as a progress report.

As to the skin test there is no doubt that this procedure induces antibody formation in many individuals. However, if one selects only subjects who are judged susceptible according to the established criteria, one finds that the frequency and height of the antibody responses increase in proportion to advance in age. Whereas in children under 5 years of age less than 20% responded, the incidence of response increased to over 80% in adults. This result seems to indicate that the skin test rarely causes *de novo* antibody formation but that one deals rather with a recall of antibodies in the majority of cases after a previous inapparent infection with mumps virus, the antibodies having disappeared over the intervening years.

In agreement with this interpretation, no conclusive evidence of protection has been obtained in outbreaks of mumps in several institutions where skin tests were applied to part of the students soon after the first cases occurred. The combined incidence of mumps in skin-tested and control groups of three schools was closely similar. Although these and other data do not exclude that *de novo* antibody formation may be obtained in some individuals, it seems more than likely that the number of these will be too small to affect significantly the course of an outbreak.

More encouraging results were obtained with subcutaneous injection of inactivated virus vaccines which permits administration of larger doses of antigen. Groups of individuals were injected with 1, 2 or 4 cc. of vaccine. The frequency and height of antibody response clearly increased with the dose. Only with 4 cc. of vaccine did all individuals develop com-

plement-fixing antibodies. Similar results were obtained with the hemagglutination inhibition test. However, some discrepancies were noted between the results of the two tests.

The role of the various antibodies measured in immunity has not been established and it is possible that other antibodies are actually responsible for resistance. It is obvious that only experience gained with these vaccines during an outbreak of the disease affords a measure of their value. A widespread epidemic of mumps occurred in southeastern Alaska 9 to 12 months after vaccination.

The incidence of mumps in the vaccinated groups was roughly half that observed in the controls (new admissions). The difference between the two groups, although definite, may not be acceptable on strict epidemiologic grounds since they had different backgrounds. However, the value of vaccination could be established in another way. By relating the antibody levels attained 4 to 5 weeks after vaccination to the incidence of mumps 9 to 12 months later, it could be seen that there existed an inverse relationship between the height of the antibody level produced and the incidence of mumps.

These results indicate then that immunity to mumps can be induced by subcutaneous vaccination with inactivated virus, that the resistance thus produced is transitory; and that the duration of immunity depends on the height of the antibody level attained. From these suggestions it is likely that more extensive protection may be achieved if the interval between vaccination and exposure is less than nine months, but whether it will be possible to immunize in the face of an epidemic in order to prevent further generations of cases or to abort the disease in individuals vaccinated shortly after exposure remains to be ascertained.

Finally, the third method, the oral spraying of attenuated active virus was studied as a possible means of inducing prolonged immunity. It was found that the Enders strains of mumps virus had lost in pathogenicity for man after about 20 passages through chick embryos. Of 410 individuals sprayed thus far only six showed minor clinical signs, mild parotitis or submaxillary adenitis which were recognized only as a result of careful checking. The children thus affected were not incapacitated.

Some antibody response was noted in from 80 to 95% of the individuals sprayed in different experiments. Antibodies appear in the serum 4 to 5 weeks after exposure to active virus, but not when inactivated virus was sprayed. Thus it is obvious that an inapparent infection results from the spray of the active attenuated agent.

The response was peculiar in that frequently antibodies to the soluble antigen exceeded those against the virus antigen. This situation is precisely that seen in the early acute stage of the natural illness. Whereas in that case antibody formation continues and both antibodies reach high levels, anti V exceeding anti S, the infection by attenuated virus appears arrested at an early stage and with it antibody formation ceases.

Here again resistance to infection will be the best measure of immunity. Permission was obtained to challenge a small group under experimental conditions and suggestive evidence of immunity was obtained also under epidemic conditions. Of four children challenged with virulent virus three months after immunization none developed mumps, whereas of six controls, four showed clinical signs of disease and the remaining gave evidence of inapparent infection, i.e., a rise in antibodies.

The epidemic in Alaska unfortunately bypassed two of the institutions where the oral spray method was used but definite exposure occurred in the third. No mumps was noted among the immunized group whereas eight cases developed among the controls.

Although these results are suggestive of protection 9 to 12 months after spraying, more extensive information is needed before the value of this procedure can be considered established. Furthermore, no information as to the duration of immunity thus induced has become available as yet.

These studies show then that there exist possibilities to induce immunity to mumps. However, the procedures are still to be considered experimental and it appears far too early to recommend them for general use and, as pointed out in the introduction, they never should be employed indiscriminately.

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PULMONARY HYALINE MEMBRANES IN NEWBORN INFANTS

Statistical, Morphologic and Experimental Study of Their Nature, Occurrence and Significance

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THE presence of membranes—variously known as asphyxial,[1-3] hyaline[4-6] or vernix membranes[7,8]—lining the alveolar ducts or alveoli has long been known to be a relatively common finding in the lungs of infants who die in the neonatal period. The majority of writers on this subject have considered these membranes to be formed of amniotic sac contents aspirated as a result of intrauterine asphyxia, and forced against the walls of air passages by air inspired after delivery. This explanation is particularly developed by Farber and Wilson,[4] who produced similar membranes in animal lungs and excised artificially ventilated human lungs by introducing a variety of liquids into the airway. However, such an interpretation has been challenged to varying degrees by a number of workers.[2,3,5,9] Recently, in a series of papers,[2,10,11] Miller and coworkers have readvanced the older suggestion[3] that these membranes are the result of a degenerative process involving the epithelium of the airway. These workers also noted, as have Arey[1] and others, that these membranes are seen relatively more frequently in the lungs of premature than of full term infants, and suggest[2] that "the hyaline material in the lungs is the result of an etiologic agent that not only injures the lung of the fetus, but causes the premature birth of the infant so injured." The obstetric implications of the suggestion that a single agent was responsible for a large proportion of premature deliveries was the chief cause of the decision to reinvestigate the problem of the nature, origin and significance of the pulmonary membranes seen in infants dying in the neonatal period.

MATERIAL AND METHODS

The autopsy protocols of all infants examined in the pathology laboratory at the Boston Lying-in Hospital during the years 1941 to 1948, inclusive, were reviewed, and microscopic slides of the lungs were studied for each case. The slides were routine sections stained with eosin-methylene blue. The number of slides available for each case varied, but was never less than 2—one from each lung. The material was obtained during 509 consecutive autopsies performed on infants. One hundred eighty-seven of the infants were stillborn and 322 were born alive. The crown-heel length was the criterion of maturity, since this measurement was the one most commonly available. The limit between prematurity and maturity was set at 47 cm.[12] The material was reviewed with particular regard for the presence of hyaline pulmonary membranes, but the presence of pulmonary hemorrhage, pneumonia, atelectasis or amniotic squamous cells was noted also. The antenatal histories were reviewed for complications of pregnancy, labor or delivery and, whenever possible, the results of gross or microscopic examination of the placenta were included in the analysis. The postnatal histories were reviewed for clinical evidences of intrauterine or extrauterine asphyxia and any use of resuscitation, oxygen inhalation or antibiotics was noted.

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In order to acquire a better concept of the nature of amniotic sac contents, 16 specimens, obtained at various stages of pregnancy, were studied. Determinations of total protein and squamous cell counts were performed and microscopic examination of sections prepared after the sediment of centrifuged amniotic fluid had been fixed in Zenker's solution was carried out for the majority of the specimens. In addition, smears of this sediment were stained by a variety of methods, and in some cases sections of the precipitate obtained by adding Zenker's solution directly to amniotic fluid were prepared.

In order to determine the relation of vernix caseosa to pulmonary hyaline membranes, masses of vernix scraped from the skin of newborn infants were fixed in Zenker's solution and sectioned. Sections of meconium from premature and full term infants were prepared also.

As a final step in analyzing the relation of amniotic sac contents to pulmonary hyaline membranes, amniotic fluid was injected intratracheally into lightly etherized rats (average weight 120 gm.). The rats were killed 6 and 24 hr. after injection, and their lungs were fixed in Zenker's solution, embedded in paraffin and stained with eosin-toluidine blue. In addition, amniotic fluid was injected intratracheally into the excised lungs of experimental animals (guinea pig and mouse); the lungs were then alternately expanded and deflated for 1 hr. by means of an air pressure line so connected that the pressure could be directed alternately to the trachea and to the chamber surrounding the lungs. After this period of "respiration," the lungs were prepared as were those of the rats.

TABLE 1

OCCURRENCE OF HYALINE PULMONARY MEMBRANES AND LARGE NUMBERS OF ASPIRATED AMNIOTIC SQUAMOUS CELLS IN RELATION TO AGE OF INFANT AT DEATH*

Age at death	Autopsies	Infants having hyaline membranes		Infants having large nos. of squamous cells
		No.	Per cent	
Stillborn	187	0		15
0 to 1 hr.	34	0		4
1 to 24 hr.	127	59	47	4
2nd day	65	26	40	1
3rd day	27	5	19	0
4th day	17	3	18	1
5th day	10	1	10	0
6 to 14 days, inclusive	30	3	10	0
Total	497	97	19	25

* Twelve infants living more than 14 days are not included.

RESULTS

Statistical Studies.—Table 1 shows the occurrence of hyaline pulmonary membranes in relation to the ages of infants at postmortem examination. Infants living more than two weeks are not included in this table. This condition, never encountered in stillborn infants and thus not arising prenatally, is seen most frequently in the lungs of infants who have died within 48 hours after delivery. Eighty-eight per cent of the patients having these membranes died during this interval.

The absence of hyaline membranes in the lungs of stillborn infants is in accord with the observations of other workers,[11] although similar material not arranged in the form of membranes has been seen in the lungs of such infants.[11, 13, 14] The absence of hyaline membranes in the lungs of infants living less than one hour is an observation of considerable significance which apparently has not been made previously, although the published data of other workers indicate the same phenomenon.[11] The absence of hyaline

TABLE 2

OCCURRENCE OF HYALINE PULMONARY MEMBRANES IN RELATION TO CROWN-HEEL LENGTH IN INFANTS LIVING 5 DAYS OR LESS

Crown-heel length, cm.	Autopsies	Infants having hyaline membranes	
		No.	Per cent
<47 (premature)	142	63	44
>47 (full term or postmature)	138	31	22
Total	280	94	34

membranes in the lungs of stillborn infants generally has been considered to indicate that air breathing is necessary for their formation. It seems, however, that air breathing must take place for a certain minimal length of time before such hyaline membranes can be formed.

Tables 2 and 3 show the occurrence of pulmonary hyaline membranes in relation to the degree of maturity. In table 3 those infants living less than one hour, presumably not long enough for these membranes to form, have not been included. Pulmonary hyaline membranes were present in roughly half of all premature infants studied. The formation of these membranes and the associated atelectasis,[5, 6, 13, 15, 16] which has been described by other workers and is discussed later in this paper, seem to represent one of the most

TABLE 3

OCCURRENCE OF HYALINE PULMONARY MEMBRANES IN RELATION TO CROWN-HEEL LENGTH IN INFANTS LIVING FROM 1 HOUR THROUGH 5 DAYS

Crown-heel length, cm.	Autopsies	Infants having hyaline membranes	
		No.	Per cent
<28	3	0	
28 to 34.9	13	5	38
35 to 40.9	27	18	67
41 to 46.9	84	40	48
>47	119	31	26

serious problems of prematurity; probably this condition is one of the main factors which keep the mortality rate of such infants at its high level.

However, the occurrence of hyaline pulmonary membranes is not restricted to premature infants. In this study they were seen at postmortem examination in 22% of the full term infants who were living at birth. Nevertheless, the lower death rate of full term infants[17] suggests that the tendency toward formation of such membranes exists much less frequently in full term than in premature infants.

Tables 1 and 4 present data on patients who had large numbers of amniotic squamous cells in the lungs. As might be expected, the majority of these infants were stillborn. It is noteworthy, however, that most of them were mature or postmature; actually 12 of the 25 infants (48%) were considered clinically to be postmature by the criteria of crown-heel length, duration of pregnancy or both. This observation does not imply, as other workers have concluded,[11] that aspiration of amniotic sac contents is most common

in mature and postmature infants, because an increase in the number of squamous cells of the amniotic fluid with increasing fetal age could also explain this phenomenon (see Studies on Amniotic Fluid, Vernix and Meconium, p. 13).

In 88 of the 93 infants who measured 30 cm. or more in crown-heel length at birth, who lived between 1 hour and 5 days, and who were found at autopsy to have pulmonary hyaline membranes, one or more of the complications of pregnancy, labor or delivery listed in table 5 were present. In the table, these are compared to the incidence of the same complications in the histories of infants of the same size and duration of life who did not have hyaline membranes at autopsy. As did tables 2 and 3, this table illustrates that hyaline membranes occur in a greater proportion of premature than of full term infants. Of particular note are the relatively greater frequency of cesarean section, fetal distress and placenta previa in the histories of infants with such membranes, these three forming 43% of complications in this group, as compared to 8% in the group who did not have hyaline membranes. Whether any of the other complications listed, many of which are generally considered capable of causing fetal anoxia in utero, have a closer

TABLE 4

OCCURRENCE OF ASPIRATION OF LARGE NUMBERS OF AMNIOTIC SQUAMOUS CELLS, IN RELATION TO CROWN-HEEL LENGTH IN INFANTS LIVING 2 WEEKS OR LESS

Crown-heel length, cm.	Infants having large nos. of squamous cells in lungs
<28	1 (anencephaly)
28 to 40.9	0
41 to 46.9	2
47 to 53.9	15
>54	7
Total	25

relation to the presence of hyaline pulmonary membranes than is demonstrated could be answered only by analysis of a larger series of infants than is available. Table 5 does not illustrate another point, the much greater frequency of congenital anomalies in the group of infants without hyaline membranes; for example, severe congenital heart disease was present in 17 (11%) of these infants, but in only 1 (1%) of infants with hyaline membranes. Similarly, other major anomalies were present in 13 (8%) of infants without hyaline membranes, but in only 3 (3%) of infants with such membranes, and, although erythroblastosis fetalis occurred with almost equal frequency in the two groups, kernicterus was present in half of those from the group without hyaline membranes, as compared to 27% of the group with such membranes. Infants with hyaline membranes thus not only had a higher incidence of certain complications capable of causing intrauterine asphyxia, but a lower incidence of lethal factors known to operate only after birth, for example, congenital heart disease and kernicterus. Failure to consider cesarean delivery as complicated delivery may have been partly responsible for the failure of some series to demonstrate a correlation between such intrauterine complications and the occurrence of pulmonary hyaline membranes,[11] since a similar correlation between fetal or neonatal asphyxia, or the presence of hyaline pulmonary membranes, and such complications has been made by many other workers.[13, 16–28]

TABLE 5

COMPLICATIONS OF PREGNANCY, LABOR OR DELIVERY IN RELATION TO OCCURRENCE OF HYALINE PULMONARY MEMBRANES

Complication	Cases with hyaline membranes (crown-heel length at birth)							Cases without hyaline membranes (crown-heel length at birth)						
	30–35	35.1–40	40.1–45	45.1–50	50.1–55	Totals	% of Complications	30–35	35.1–40	40.1–45	45.1–50	50.1–55	Totals	% of all Complications
Maternal heart or kidney disease	0	2	1	0	0	3	3	1	0	0	2	0	3	2
Diabetes	0	0	1	0	2	3	3	0	0	1	0	0	1	1
Toxemia, all types	0	3	8	1	0	12	13	2	1	9	2	4	18	10
Multiple pregnancy	0	3	3	0	0	6	6	0	2	9	2	0	13	7
Erythroblastosis fetalis	0	0	4	4	3	11	12	0	1	3	18	5	27	15
Induction	0	0	2	5	1	8	9	1	1	2	10	7	21	12
Premature rupture of membranes	0	0	1	0	0	1	1	1	3	3	0	0	7	4
Premature separation of placenta	1	1	3	0	0	5	5	0	4	2	1	1	8	5
Premature labor only	2	3	5	3	0	13	14	2	4	14	5	0	25	14
Prolonged labor	0	0	1	0	0	1	1	0	0	0	1	2	3	2
Dystocia, all causes	0	0	2	2	1	5	5	0	0	0	4	3	7	4
Placenta previa	1	0	5	3	0	9	10	0	1	2	0	0	3	2
Precipitate delivery	0	1	0	0	0	1	1	0	0	0	0	0	1	1
Fetal distress	0	0	1	2	3	6	6	0	0	0	0	0	0	0
Cord around neck or shoulder	0	0	1	0	0	1	1	0	0	0	5	0	5	3
Prolapsed cord	0	0	0	0	0	0	0	0	0	0	1	3	4	2
Version (internal)	1	0	1	0	0	2	2	0	1	1	0	1	3	2
Breech delivery	0	5	3	1	0	9	10	0	1	8	2	5	16	9
Cesarean section	0	3	12	7	3	25	27	2	1	4	2	2	11	6
Normal delivery	0	0	0	3	2	5		0	0	0	16	16	32	
Total complications	5	21	54	28	13	121		10	20	58	55	33	176	
Total infants	5	18	35	23	12	93		6	13	36	60	42	157	
% with complications	100	100	100	87	83	95		100	100	100	73	62	80	

TABLE 6

OCCURRENCE OF PULMONARY HYALINE MEMBRANES IN PREMATURE AND FULL TERM INFANTS DELIVERED BY CESAREAN SECTION*

Crown-heel length, cm.	Autopsies	Infants having hyaline membranes	
		No.	Per cent
28 to 46.9	25	18	72
>47	15	10	67
Total	40	28	70

* These infants were alive at birth and lived for from 1 hr. through 5 days.

Table 6 shows the frequency of pulmonary hyaline membranes at postmortem examination in infants delivered by cesarean section. Reasons for section in these cases were: toxemia 10 cases, placenta previa 7, disproportion 6, erythroblastosis fetalis 2, maternal heart disease 2 and fetal distress 1 case. Whether the high incidence of such membranes in this group of infants is the result of section itself or of the condition providing the indication for operation is difficult to determine, but in most of these cases a significant complication of pregnancy, labor or delivery was present. However, the fact that 10 of the 31 full term infants with pulmonary hyaline membranes were delivered by cesarean section, a ratio out of proportion to the incidence of cesarean section,[29] strongly suggests that cesarean section itself is a significant factor in the production of these hyaline membranes.

TABLE 7

OCCURRENCE OF PNEUMONITIS AND PULMONARY HEMORRHAGE IN NEWBORN INFANTS LIVING FOR FROM 1 HOUR THROUGH 5 DAYS

	Autopsies	Complications			
		Pneumonitis		Pulmonary hemorrhage	
		No.	Per cent	No.	Per cent
Infants having hyaline membranes	94	26	29.8	43	45
Infants not having hyaline membranes	149	45	30.2	81	54

Table 7 shows that pulmonary hyaline membranes often are associated with pneumonitis and pulmonary hemorrhage but that in many instances they occur in the absence of either pneumonitis or pulmonary hemorrhage. Thus, these processes are not necessary factors in the genesis of these membranes and they may more reasonably be considered as parallel or secondary phenomena.

Evidences of more or less severe anoxia were seen in all infants having hyaline membranes. In 64 (68%) of the 94 infants with pulmonary hyaline membranes who died during the first five days of life, no other condition considered capable of explaining death was found. Congenital malformations were observed in 3 of the remaining infants, intracranial hemorrhage in 15 and erythroblastosis fetalis in 12, but even in some of these 30 cases the pulmonary condition seemed to be the major cause of death.

Microscopic Study of Pulmonary Haline Membranes.—The typical appearance of the pulmonary hyaline membranes[2-6, 7, 8, 11, 13, 14, 30, 31] of newborn infants is shown in Figs. 1-3. It has been described previously by many workers. The membranes are acidophilic and usually homogeneous and hyaline. They contain amniotic squamous cells and fat, the amount of the former, and apparently also of the latter, increasing with the duration of pregnancy.[2] The frequency with which the membranes are observed to overlie an intact bronchiolar lining (Fig. 2a) or to be separated by squamous cells from the wall of the air passage (Fig. 2b) seems to be strong evidence against the theory that their formation results from degeneration of the epithelium of the airway. Moreover, squamous cells are often seen within the membrane itself (Fig. 3a).

FIG. 1. Low power view of lung of premature infant showing hyaline membranes lining alveolar ducts and alveoli. Membranes block mouths of many alveoli. Note absence of edema, hemorrhage or inflammation. (Hematoxylin and eosin, ×125.)

Many of the sections studied illustrated the probable mechanism of formation of these membranes. Small bronchioles often were completely plugged by masses of hyaline acidophilic material (Fig. 3b) or lined by hyaline membranes. In many instances, as in that illustrated, the mass of material appeared too great to be accounted for by a degenerative change in the bronchiolar epithelium and, as stated previously, the intact epithelium often was visible beneath these masses. Similar observations have been described by other workers.[5, 31] Supposedly these bronchiolar contents come from above, and the next phase probably is the movement of this material downward into alveolar ducts where it is flattened around the wall in the form of a hyaline membrane. The essential role of air breathing in this process is apparent from table 1, and the factor of respiration in the

formation of similar membranes from a liquid in the airway has been demonstrated by other workers.[4]

As figures 1 and 3b show, pulmonary hyaline membranes often are most numerous in alveolar ducts and appear to seal off the mouths of alveoli and prevent them from expanding. The difficulty of demonstrating the epithelium of normal alveolar ducts[12, 32–34] is partly responsible for the conclusion by other workers that these membranes are formed from degenerated epithelium of the airway.[2, 3] Misinterpretation of the patchy unexpansion

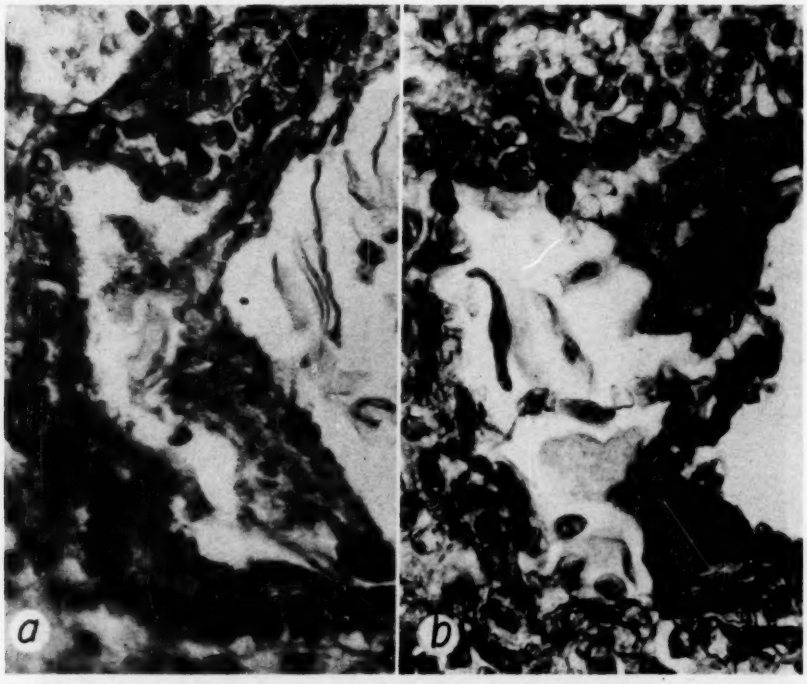

FIG. 2a. Acidophilic membrane covering intact bronchiolar epithelium, with squamous cells in lumen, incorporated in membrane and lying between membrane and epithelium. (Hematoxylin and eosin, ×550.) b. Hyaline membrane with squamous cells lying between membrane and alveolar wall. (Hematoxylin and eosin, ×700.)

of the lung resulting from the sealing off of alveolar mouths by membranes in alveolar ducts appears to be partly responsible for the concept of "congenital alveolar dysplasia,"[9] no instances of which were found in this study. This combination of pulmonary hyaline membranes and atelectasis, presumably secondary to blocking of alveolar mouths, was the most common microscopic observation in lungs which were thought to be atelectatic on gross examination. Simple atelectasis (lack of expansion) was extremely rare in the lungs of infants who were living at birth.

The concept that the pulmonary hyaline membranes, once formed, can cause progressive atelectasis provides the best available explanation for the common clinical observation that infants who have aspirated amniotic sac contents often have a brief period of relative well-being before the development of respiratory distress leading to death.[5, 25, 27, 28, 35–37]

This same phenomenon is described as a typical clinical feature of "congenital alveolar dysplasia," although the mechanism is difficult to understand if the lungs are truly unexpandable.[9]

Studies on Amniotic Fluid, Vernix and Meconium.—The results of the squamous cell counts and the determinations of the total protein content of 16 specimens of amniotic fluid are given in chart 1. The number of specimens is too small to give a complete picture of the rise in the number of amniotic squamous cells during the period of gestation, but study shows that such a rise exists and that probably it is greatest in the last

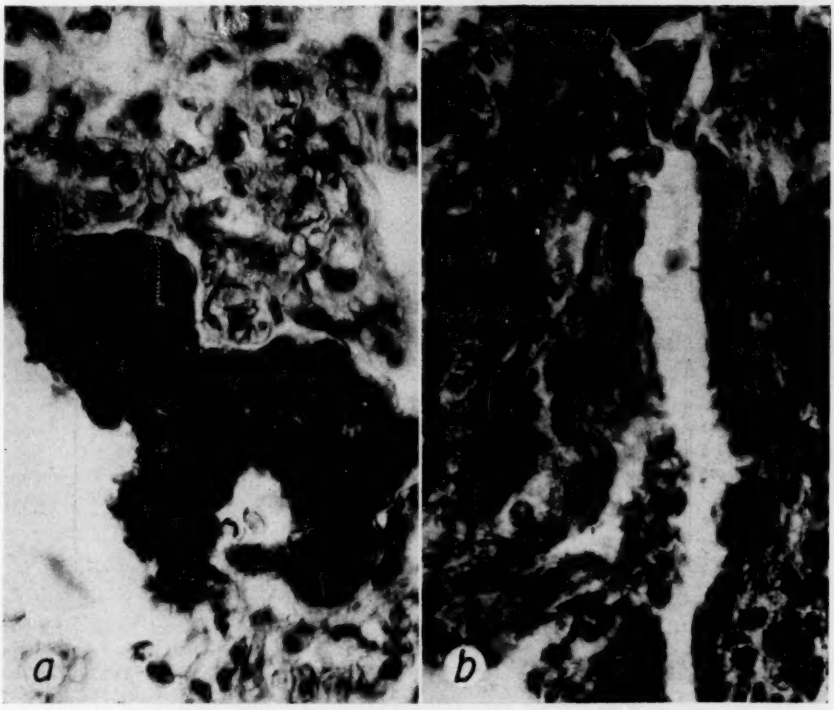

FIG. 3a. Thick hyaline membrane in alveolar duct, blocking alveolar mouth. Note squamous cell within membrane. (Hematoxylin and eosin, ×700.) b. Hyaline material occluding junction of bronchiole with alveolar duct. (Hematoxylin and eosin, ×550.)

part of pregnancy. Thus the low number of squamous cells in the lungs of many infants with pulmonary hyaline membranes does not indicate that significant aspiration of amniotic sac contents has not taken place, because the majority of patients with such membranes are premature infants.

The rise in the number of squamous cells in the amniotic sac contents during the last trimester is reflected in the microscopic appearance of the fixed centrifuged sediments. Sediment from sac contents obtained during the early part of pregnancy contains a relatively small number of squamous cells and much granular acidophilic protein material (Fig. 4a), whereas that from sac contents obtained in the latter part of pregnancy contains similar protein material, but a relatively large number of squamous cells (Fig. 4b). The

total protein content was remarkably low in some of the samples taken early in pregnancy, but the variations in the third trimester were less noticeable and less consistent than was the change in squamous cell count.

Figure 5 shows a section of vernix caseosa scraped from the skin of a normal newborn full term infant. It is composed chiefly of squamous cells, the fat having been removed by the usual method of dehydration by passage of tissue through fat solvents. Microscopically, vernix from premature infants is identical with that from full term infants, although the amount present is much less. Although a certain amount of fat can be demonstrated in

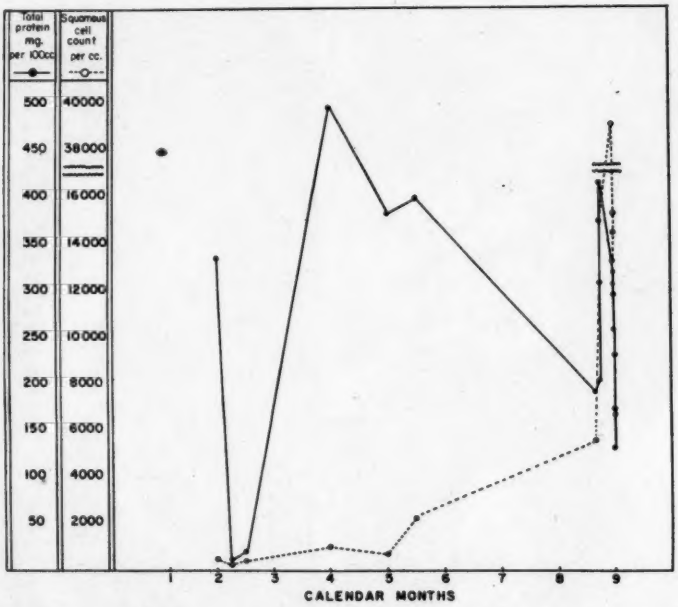

CHART 1. Total protein (mg./100 cc. amniotic fluid) and squamous cell count (cells/cc.) plotted against duration of pregnancy in calendar months. Tendency of squamous cell count to rise during last month of pregnancy is well shown; total protein content varies widely but remains in same range as in earlier months.

hyaline membranes, fat is not a major component, since the membranes retain their dense, homogeneous structure after passage through fat solvents. Squamous cells may be present, but rarely to th extent seen in sections of vernix. Thus, the pulmonary hyaline membranes do not consist to any significant degree of vernix caseosa.

Sections of meconium obtained at postmortem examination from the intestines of newborn infants were studied also. Meconium consists of concentrated swallowed amniotic sac contents mixed with mucus and other matter secreted by the intestinal tract; in premature infants it consists of amorphous acidophilic matter rarely containing squamous cells (Fig. 6a), whereas in full term infants it contains large numbers of squamous cells (Fig. 6b). Although in routine sections the appearance of meconium from premature infants is such that one might suspect these membranes to be formed of it, the membranes do not contain mucus, as shown by special stains, whereas meconium contains large amounts. Thus, the membranes are not composed of aspirated meconium either.

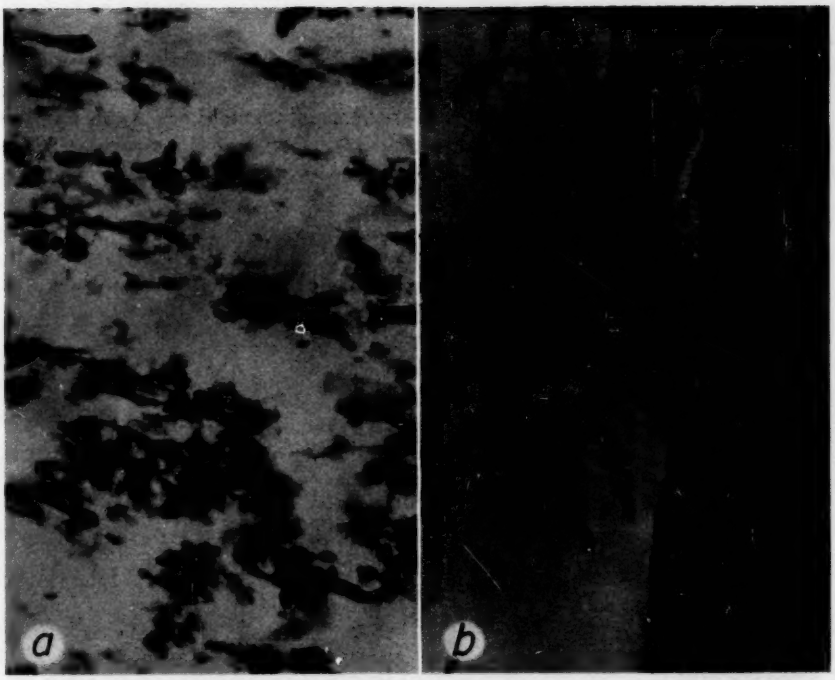

FIG. 4a. Section of sediment from amniotic fluid obtained during second trimester of pregnancy showing much granular acidophilic protein and scattered squamous cells. (Hematoxylin and eosin, ×550.) b. Section of sediment from amniotic fluid obtained at term showing relatively smaller amount of protein material and relatively larger number of squamous cells. (Hematoxylin and eosin, ×550.)

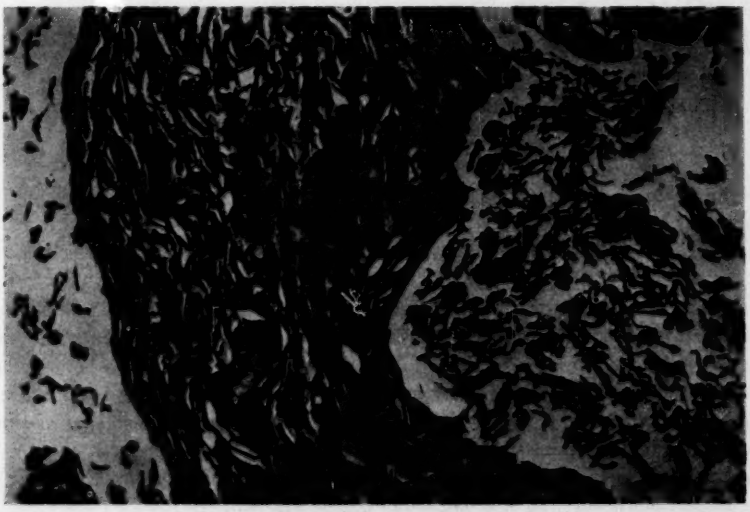

FIG. 5. Section of vernix from full term infant showing closely packed squamous cells. (Hematoxylin and eosin, ×120.)

Sections of the lungs showing pulmonary hyaline membranes stained by a variety of methods and the colors of the membranes were compared to those of the other tissue components and to sections of fixed amniotic fluid sediment stained by the same methods. The following stains were used: eosin-methylene blue; eosin-toluidine blue; eosin-hematoxylin; Mallory's aniline blue: Lee-Brown modification of Mallory's aniline blue; Papanicolaou; van Gieson; Mallory's phosphotungstic acid hematoxylin; Verhoeff's elastic tissue stain. Although such an analysis could not be expected to demonstrate conclusively the nature of the material composing the hyaline membranes, it was apparent that the membranes did not give color reactions typical of serum protein, red cells, mucus or

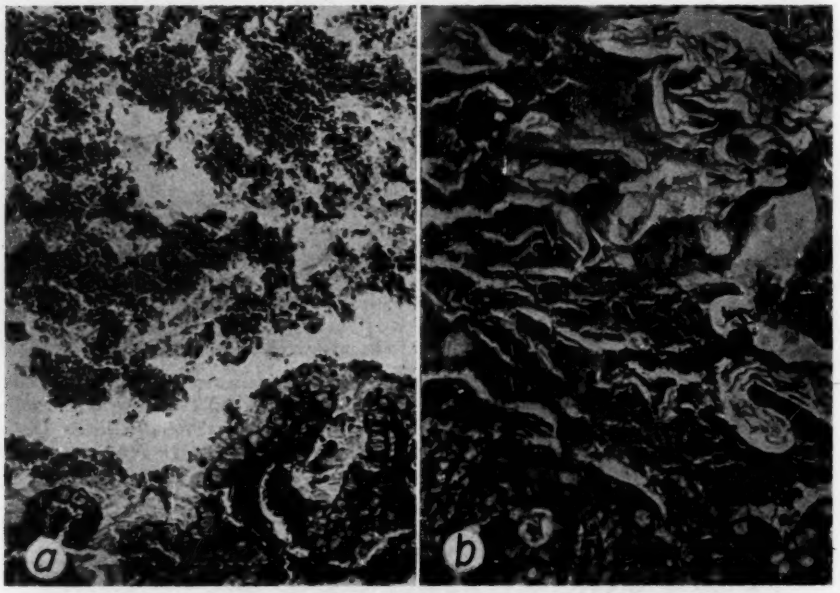

FIG. 6a. Section of colon of premature infant showing meconium consisting of mucus mixed with acidophilic granular debris. One squamous cell is present in section. (Hematoxylin and eosin, ×120.) b. Section of colon of full term infant showing meconium consisting of mucus, acidophilic granular material and large numbers of squamous cells. (Hematoxylin and eosin, ×120.)

bronchiolar epithelium, whereas their color was consistent with that of concentrated amniotic fluid protein.

EXPERIMENTAL PRODUCTION OF HYALINE PULMONARY MEMBRANE

In the past, a number of workers have been unsuccessful in attempts to produce hyaline pulmonary membranes by intratracheal injection of amniotic sac contents into excised lungs or into living animals.[8, 38] Two factors demonstrated previously to be important in the production of hyaline pulmonary membranes in newborn infants—air breathing for at least one hour and the necessity of concentrating a relatively large amount of amniotic fluid—have not been appreciated and taken into account in these studies.

In this study, amounts of human amniotic sac contents varying from 0.5 to 2 cc. were injected intratracheally into 120 gm. white rats which had been lightly anesthetized with

ether. Six rats were killed 6 hours after injection, and 6 were killed 24 hours after injection. Hyaline pulmonary membranes were not seen in sections of any of the lungs.

On the other hand, 15 to 20 cc. of fluid from the amniotic sac of full term infants were injected intratracheally in 1 cc. amounts into excised adult guinea pig and mouse lungs

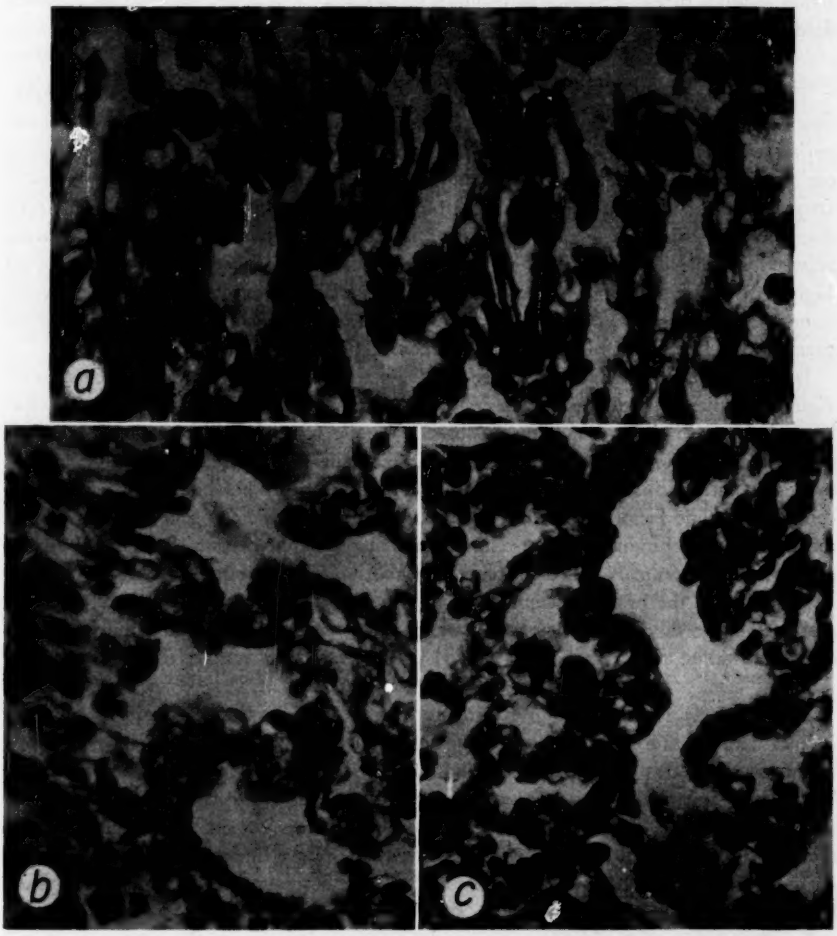

FIG. 7a. Guinea pig lung, after intratracheal administration of amniotic fluid, showing squamous cells in alveoli. (Hematoxylin and eosin, x600.) b and c. Guinea pig lung, after intratracheal administration of amniotic fluid, showing thin hyaline membranes lining alveolar ducts. (Hematoxylin and eosin, ×600.)

while the lungs were alternately expanded and contracted for one hour by air pressure applied to the trachea and then to the vessel containing the lungs. A pressure of 1 pound (50 mm.Hg) was used, and the lungs were expanded and contracted 20 times per minute. In sections of these lungs, amniotic squamous cells could be seen in small clusters in alveoli (Fig. 7a) or in membrane formation around the walls of alveoli, while thin

hyaline acidophilic membranes were seen in some alveoli (Fig. 7b and c). Thus it is apparent that, if sufficient amniotic fluid is introduced into the airway and if respiration is continued for a sufficient length of time after the injection, pulmonary membranes similar to those seen in newborn human infants can be produced. Failure to accomplish this in living animals probably is due to inability to introduce a sufficient quantity of amniotic fluid.

Discussion

The statistical data presented demonstrate a high incidence of complications of pregnancy, labor or delivery capable of causing fetal anoxia in patients dying in the neonatal period with pulmonary hyaline membranes. In a great many cases these complications can cause premature delivery. Since these membranes occur with significantly greater frequency in premature infants than in full term infants and since it is reasonable to argue that premature delivery implies significant intrauterine anoxia, actually the correlation between intrauterine anoxia and the presence of hyaline membranes may well be even higher than any study has succeeded in demonstrating. From this material, it seems unnecessary to assume a hidden factor of unknown character to be the etiologic agent of premature delivery, the production of pulmonary hyaline membranes or both.

It has been demonstrated repeatedly by earlier workers that anoxia of the fetus causes vigorous respiratory movements with definite aspiration of amniotic sac contents.[39–47] It has been shown also that pulmonary membranes can be formed from a variety of liquids introduced into the lungs.[4,5] The inability of earlier investigators to produce such membranes by introducing amniotic fluid intratracheally probably has been due to failure to consider the time factor involved in the process. In this study homogeneous, eosinophilic membranes were produced by introducing amniotic sac contents into the excised airway of experimental animals and then ventilating the lungs for one hour. These membranes were similar to the hyaline membranes found in the lungs of newborn infants. Furthermore, amniotic fluid sediment was shown to have staining properties similar to those of these hyaline membranes, whereas red cells, serum and various tissue components did not.

The relatively low number of squamous cells in the lungs of the majority of these infants with hyaline membranes is adequately explained by the predominant occurrence of this condition in premature infants whose amniotic fluid has a low squamous cell count. The hyaline membranes are composed predominantly of protein, which the evidence indicates is protein of the amniotic fluid. Since the protein content of this fluid is relatively low, considerable water must be removed to produce the concentration of protein in these dense homogeneous membranes. However, several investigators have demonstrated the ability of the fetal lung to absorb water to the degree indicated.[41–50]

Results of this study do not permit a definitive explanation of the predominance of pulmonary hyaline membranes in premature infants dying in the neonatal period. It is entirely reasonable that factors producing fetal anoxia are more common in the pregnancy, labor or delivery of such patients than in those of full term infants. It also seems probable that premature infants are less able to dispose of aspirated amniotic sac contents (by absorption and via the airway) than are full term infants.

Summary

The results of statistical, morphologic and experimental studies on the nature, occurrence and significance of hyaline (asphyxial) membranes seen in the lungs of infants

who die in the neonatal period are presented. Analysis of material from 509 consecutive autopsies on newborn infants, together with analysis of the infants' histories, shows that these membranes occur most commonly in premature infants and in more mature infants with a history of a complication of pregnancy, labor or delivery capable of causing fetal anoxia. These hyaline membranes are not seen in stillborn infants nor in infants living less than one hour. They appear to cause atelectasis, by blocking the mouth of alveoli, and to be a major cause of death in the neonatal period.

Studies on vernix, meconium and amniotic fluid indicate that these hyaline membranes are not formed of vernix or meconium, but of the concentrated protein of aspirated amniotic fluid. A rise in the squamous cell content of amniotic fluid during the third trimester of pregnancy is demonstrated; this may explain the difference in microscopic appearance between hyaline membranes formed of amniotic fluid which is aspirated before this rise in squamous cells takes place and those containing squamous cells which are seen if the fluid is aspirated after this increase occurs. The membranes are demonstrated to be independent of pulmonary hemorrhage, edema or inflammation and not to be formed of degenerated airway epithelium.

Similar membranes were produced experimentally by repeated intratracheal injection of small amounts of amniotic fluid into the excised respiratory tracts of animals while the lungs were alternately expanded and contracted for one hour. The time and volume factors necessary for successful experimental production of these membranes are discussed.

The significance of pulmonary hyaline membranes in the production of neonatal atelectasis is indicated. No instances of "congenital alveolar dysplasia" were found in the 509 cases reviewed, and evidence that it may not be a valid clinical and pathologic entity is presented.

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SPANISH ABSTRACT

Membranas Hialinas Pulmonares en el Recién Nacido; Estudio Estadístico, Morfológico y Experimental Sobre su Origen, Ocurrencia y Significación

Se presentan los resultados del estudio de 509 necropsias consecutivas realizadas en recién nacidos y fetos (stillborn) en relación con la ocurrencia de membranas hialinas pulmonares. Estas membranas ocurren más frecuentemente en niños prematuros y niños a término con historia de alguna complicación durante el embarazo o el parto capaz de producir una asfixia intrauterina. El análisis de los resultados de las distintas técnicas de coloraciones anatomopatológicas indicó que estas membranas no son formadas de epitelios degenerados de las vías respiratorias. La inyección experimental de líquido anniótico en la tráquea de animales con pulmones ventilados artificialmente da lugar a la producción de membranas similares a las observadas en los recién nacidos. Los autores estiman que las membranas hialinas pulmonares observadas en los recién nacidos son producidas por el líquido anniótico aspirado a consecuencia de una asfixia intrauterina.

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PITUITARY ADRENOCORTICOTROPIC HORMONE (ACTH) AND 11-DEHYDRO 17 HYDROXY CORTICOSTERONE (CORTISONE) THERAPY IN THE LEUKEMIAS AND LYMPHOMAS OF CHILDREN

By C. E. SNELLING, M.B., W. L. DONOHUE, M.D., BERNARD LASKI, M.D., F.R.C.P. (C), AND S. H. JACKSON, PH.D.
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THIS report is concerned with the results obtained in the treatment of 16 cases of leukemia and one case of lymphosarcoma with either ACTH or cortisone.* All the cases, in addition to the more specific hormone therapy, received as adjuvants blood transfusions, antibiotics and symptomatic treatment as indicated. Several cases had been previously treated with one of the folic acid antagonists (aminopterin®). In 13 patients the primary hormone treatment was with ACTH and with four patients, cortisone was initially used. When relapses occurred in most cases a further course of treatment was given using either the original hormone or the alternative, depending chiefly on the available supply. Aminopterin® was used in a few patients who were refractory to further hormone therapy following the initial relapse.

The 17 cases treated are summarized in table 1 on the opposite page. Six of the eight patients who received ACTH prior to any other form of specific treatment had a complete remission which lasted from 3 to 13 weeks before relapse occurred. Two of these patients, Case 8 (A.T.) and Case 9 (B.J.), are still completely normal, both hematologically and clinically, 10 and 11 weeks, respectively, after cessation of treatment. Their hemoglobins have been maintained and there has been no significant reappearance of blast cells in the bone marrow. In the remaining two patients, one, Case 6 (V.LaC.), had only a very slight response despite large doses of ACTH and as soon as therapy was halted, his leukemia rapidly progressed, and the other, Case 12 (F.F.), showed no effect, the child dying on the fourth day of therapy from a cerebral hemorrhage.

In the five patients who received aminopterin® prior to ACTH therapy, one, Case 5 (E.M.), had a complete remission which lasted 10 weeks. Another, Case 11 (D.S.), had a partial hematologic response but developed generalized sepsis while on treatment with ACTH and died. Two, Case 2 (L.P.) and Case 3 (L.M.), had a moderate or slight remission which quickly relapsed and the fifth patient, Case 13 (El.M.), showed no response and died on the fourth day of treatment with ACTH from an intestinal haemorrhage.

Five of the children who have relapsed have been retreated with ACTH and only

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* ACTH was obtained from the Armour Laboratories, Chicago, and the cortisone from Merck & Co., Montreal.

TABLE 1

Summary of Clinical and Hematologic Results

Case	Age	Sex	Type*	Total Treatment mg./days	Result from Hormone Therapy	Total Retreatment mg./days	Result of Retreatment
1. W.B.	7	M	E	ACTH 1180/23	Complete remission—13 wk. Mild relapse.	ACTH 1000/23	Complete remission—lasted 6 wk. and then relapse; now under treatment with ACTH.
2. L.P.	3	F	A	Aminopterin (R) 53/147 ACTH 1610/36	Moderate remission—2 wk. Relapse.	ACTH 440/6	No response—died.
3. L.M.	8	F	A	Aminopterin (R) 44/74 ACTH 980/23	Slight remission—died.		
4. J.C.	2	M	A	ACTH 680/24	Complete remission—3 wk.	ACTH 1560/20 Cortisone 1400/14 Aminopterin (R) 2.5/10	No response—died.
5. E.M.	4	M	A	Aminopterin (R) 32/52 ACTH 900/16	Complete remission—10 wk.	ACTH 2420/31	No response. On aminopterin (R) now.
6. ULaC	14	M	L	ACTH 2020/20	Slight remission—died.		
7. G.W.	3½	M	L	ACTH 1030/19	Complete remission—3 wk.	ACTH 1030/15 Cortisone 2200/12 Aminopterin (R)	No response—died.
8. A.T.	12	M	A	ACTH 2300/33	Complete remission—no relapse after 10 wk.		
9. B.J.	4	F	A	ACTH 880/17	Complete remission—no relapse after 11 wk.		
10. E.K.	4	M	A	ACTH 1360/25	Complete remission—5 wk. Mild relapse.	Being treated with ACTH	
11. D.S.	2	F	A	Aminopterin (R) 9/22 ACTH 1120/18	Good hematologic response but became jaundiced. Died.		
12. F.F.	7	F	L	ACTH 320/4	Died from cerebral haemorrhage on 4th day of treatment.		
13. El.M.	3	F	A	Aminopterin (R) 7/7 ACTH 340/4	Died from intestinal haemorrhage on 4th day of treatment.		
14. B.K.	3	M	L	Cortisone 1900/13	No response—died.		
15. D.K.	5	M	L	Cortisone 2000/15	Complete remission—4 wk.	ACTH 1740/22 Aminopterin (R) 8/8	No response. Died.
16. W.W.	8	M	L	Cortisone 400/4	No response—died on 4th day.		
17. D.B.	4	M	L.S.	Cortisone 3000/16	Excellent response—recurrence in 2 wk. Died.		

* Type: E—Eosinophilic
A—Aleukemic
L—Leukemic
LS—Lymphosarcoma

one of these, Case 1 (W.B.), had favourable response. He had a complete second remission which lasted six weeks, although his response at this time was more sluggish than during his first treatment. He proved completely refractory to further treatment and has since died. The other four patients showed no response to retreatment with ACTH and they were also refractory to other types of therapy such as cortisone and aminopterin®.

The length of treatment in those patients with an initial good response varied from 17 days (Case 9 [B.J.]) to 33 days (Case 8 [A.T.]), this being the length of time re-

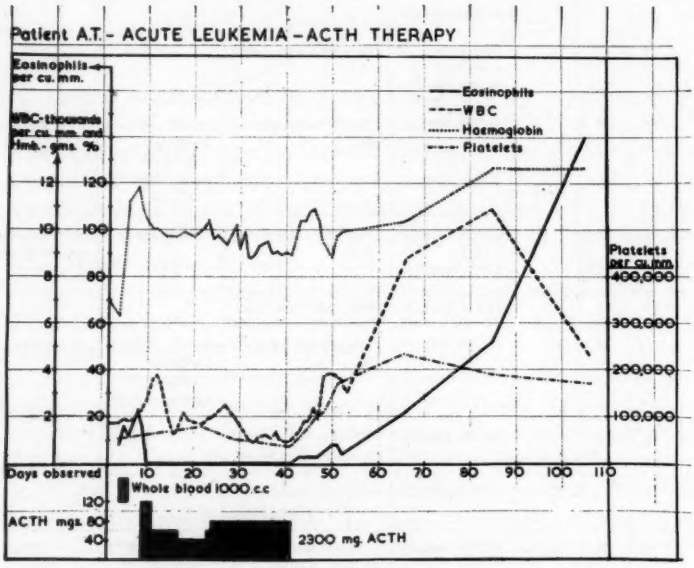

CHART 1. Case 8 (A.T.). Aleukemic type of leukemia. Changes in peripheral blood coincident with remission are obvious.

quired to produce a normal marrow. The total amount of ACTH given varied from 680 mg. (Case 4 [J.C.]) to 2300 mg. (Case 8 [A.T.]). Dosage varied from 20 mg./day in the youngest case (Case 4 [J.C.]) to 200 mg. in the oldest (Case 6 [U.LaC.]). On the basis of the eosinophil counts and the response of the patients it was judged that the smaller dosages were ineffective and it was eventually decided that initial doses of 80 to 120 mg./day were needed with a usual decrease of 40 to 60 mg. in the later stages of treatment. It might also be noted that the largest doses given in Case 6 (U.LaC.) had very little effect.

Four patients received cortisone as their primary treatment; three of these were leukemia cases and the fourth, Case 17 (D.B.), a case of abdominal lymphosarcoma. Of the three patients with leukemia, one, Case 15 (D.K.), had a complete remission, while the other two showed no response, one, Case 16 (W.W.), dying on the fourth day of treatment and the other, Case 14 (B.K.), on the 13th day of treatment. The successfully treated child received 2,000 mg. over a period of 15 days. His remission lasted four weeks and was followed by a relapse which was refractory to treatment with both ACTH and aminopterin®.

The case of lymphosarcoma responded extremely well with much shrinkage of the tumour masses and disappearance of symptoms. However, two weeks following cessation of treatment there was an exacerbation of the disease which was quickly followed by death.

The hematologic observations in Case 8 (A. T.) are shown in charts 1 and 2. This boy had a relatively long remission following ACTH therapy. Similar observations in respect of Case 15 (D. K.) are depicted in charts 3 and 4. In this child there was a complete but very short remission following the administration of cortisone.

Biochemical Observations

Biochemical studies were made on nine patients from whom satisfactory urine collections could be obtained (see table 2).

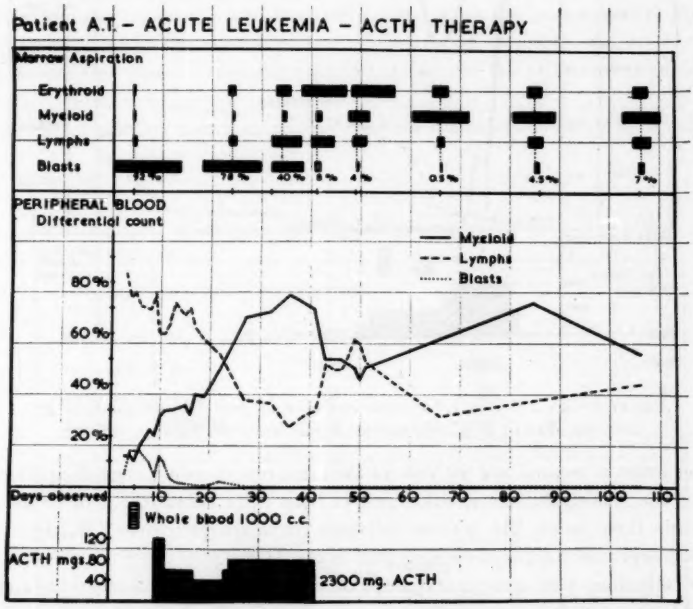

Chart 2. Case 8 (A.T.). At top of chart are shown percentages of various cell types in marrow. Reduction in proportion of blast cells and reversal of marrow to normal is well demonstrated. Interesting feature is reappearance of erythroid elements before those of granulocytic series. In lower half of chart are recorded changes in peripheral differential counts.

Blood serum was examined weekly for sodium, potassium, chloride, calcium, inorganic phosphorus and alkaline phosphatase. Weekly glucose tolerance tests were also done. The sodium and chloride remained within normal limits. The serum K was usually reduced during active treatment, frequently in the range of 3.5 to 4.5 mEq./l. (normal 4.5 to 5.5 mEq./l.) occasionally falling to 3.0 or lower. The Ca remained normal or slightly elevated with the average being in the high normal zone. The inorganic P was usually low during active treatment, most of the determinations falling in the range of 3.0 to 4.5 mg./100 cc. (normal 4.5 to 5.5 mg./100 cc.). No consistent effect on the alkaline phosphatase was observed. The glucose tolerance curve was usually slightly diabetic in nature. The fasting blood sugar was frequently 10 to 20 mg./100 cc. above

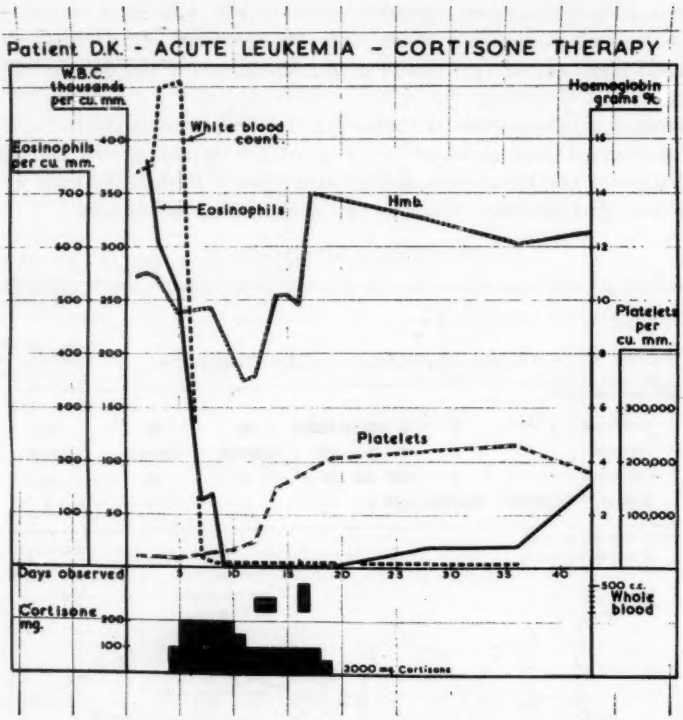

CHART 3. Case 15 (D.K.). Complete remission of short duration produced by cortisone. Fall in WBC and increase in number of platelets are striking.

the upper limits of normal and the peak of the curve rose to values as much as 40 mg./100 cc. above the maximum normal value and in most cases failed to return to the fasting level within three hours. The glucose tolerance curve always returned to normal within one or two days after stopping administration of the ACTH.

Urine collections were made continuously on some patients and on others the collections were made for a 48 hour period once a week. A base period of at least three days was obtained on each patient before commencing treatment, and subsequent variations observed during treatment were evaluated by comparison with the observations made at that time. Determinations were made of Na, K, Cl, total urinary N, uric acid, creatine, creatinine, and 17-ketosteroids. These results were expressed as the total excretion in 24 hours.

It was observed that the creatinine excretion was constant for each patient and was not affected by the course of the disease or the treatment. The values for the other constituents were then expressed as the amount excreted/gm. creatinine. When this was done, a good many variations attributable to size of the patient and unavoidable irregularities in urine collections were minimized and the results were more clearly interpreted.

It is not considered advisable to include in this report all the mass of data obtained. After studying the results, certain correlations or lack of correlation between the biochemical findings and the hematologic and clinical progress of the patients became apparent (see table 2).

The rate of excretion of uric acid paralleled the rate of apparent destruction of peripheral leukemic cells very closely in almost all cases (column 1, table 2). In those cases where the white blood cell count was relatively low and varied within fairly narrow limits, the uric acid excretion was low and fairly constant. It seems probable, therefore, that the excessive uric acid excretion arose from the destruction of leukemic tissue.

The rise in the creatine excretion lagged a few days behind the uric acid excretion, but also appeared to parallel the rate of destruction of the leukemic cells particularly the blast forms in the bone marrow (column 2). A close comparison is difficult as marrow examinations were not done as frequently as the white counts. The decrease in blast cells in the marrow apparently was never so precipitous as the fall in the peripheral white blood cell count; and in those cases in which a remission was produced, it usually came about only after a week or more of treatment. Similarly, the rise in creatine excretion was also slow, and the variations were frequently, but not always, in a narrower range than that of the uric acid. The typical picture when a good remission was obtained was a rise in the creatine about a week after the initial rise and fall of the uric acid, and coinciding with a drop in the marrow blast cells.

While the parallelism between creatine excretion and elimination of blast cells in the

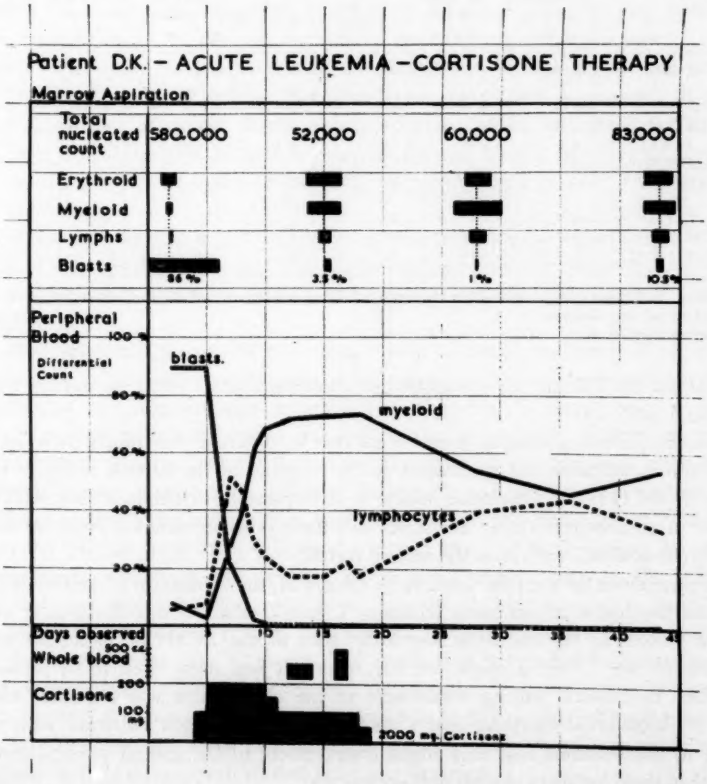

CHART 4. Case 15 (D.K.). At top of chart are shown percentages of various cell types in marrow, demonstrating almost complete elimination of blast forms and their reappearance approximately 3 wk. after cessation of treatment.

marrow was not as clear as that between uric acid excretion and the destruction of peripheral leukemic cells, these two effects do appear to be related. The marrow blast cells may be the source of the creatine or the creatine may arise from another process such as glyconeogenesis, occurring simultaneously with the destruction of leukemic cells.

Another effect usually observed during the administration of ACTH is marked retention of Na and a less marked excretion of K. This did not occur in all cases and seemed to bear little or no relation to the effectiveness of the treatment. Therefore, salt retention has no apparent connection with the effectiveness of the treatment and hence it is likely that the corticoid or corticoids that result in a remission of the leukemic process are not those concerned with salt balance. There was also no relationship between the

TABLE 2

CORRELATIONS OF BIOCHEMISTRY WITH CLINICAL AND HEMATOLOGIC OBSERVATIONS IN CASES TREATED WITH ACTH OR CORTISONE

Case No.	1 Increased Uric Acid Excretion vs. Drop in W.C.	2 Increased Creatine vs. Drop in % Blasts	3 Salt Retention vs. Remission		4 Increased N_2 Excretion vs. Remission		5 17-KS vs. Salt Retention		6 17-KS vs. N_2 Excretion		7 17-KS vs. Remission	
X (EK)	++	+	0		+		0		+		++	
			1st	2nd	1st	2nd	1st	2nd	1st	2nd	1st	2nd
VII (GW)*	++	+	0	−	++	++	0	−	++	++	++	++
III (LM)	++	+	−		+		0		++		+	
I (WB)	++	++	++		++		++		++		+	
XVI (WW)†	++	−	−		−		−		−		−	
IX (BJ)	+	++	+		0		0		+		0	
		2nd										
V (EM)*	+	0	0		−		0		++		−	
VIII (AT)	++	++	0		+		0		+		++	
XVII (DB)†‡	++	++	0		0		+		0		++	

* Chemical studies were undertaken during both 1st and 2nd courses of treatment with GW but only to 2nd course with EM.
† Cases treated with cortisone.
‡ Lymphosarcoma of cecum.

effect of the ACTH on the 17-ketosteroid excretion and its effect on sodium retention (column 5, table 2).

From the preceding data, it would seem that in different individuals there are variations, both quantitative and qualitative, in the response of the adrenal cortex to stimulation with ACTH. An alternative which it is impossible to check is that ACTH is a mixture of adrenocorticotropic hormones and there is some variation from lot to lot in regard to its qualitative effect on the adrenal cortex.

The parallelism between the increase in urinary N, the increase in 17-ketosteroid excretion, and the degree of remission (columns 4, and 7, table 2) was close; there were the two exceptions. In the one there was little effect of the ACTH on either the nitrogen excretion or the 17-ketosteroids, but the treatment was most effective in producing a remission. In contrast, during retreatment in the other, there was a marked elevation in the 17-ketosteroid excretion and a doubling of the nitrogen excretion with no real change in the leukemia and only slight improvement in his general physical condition. Other than these instances, the parallelism was good.

This parallelism would lead one to suspect that the increase of 17-ketosteroids arises

from the corticoids concerned with glyconeogenesis and that these corticoids are also in some way connected with the limitation of the leukemic process.

Discussion

As early as 1942, Heilman and Kendall[1] had observed temporary regression of a lymphoid tumor in mice with the administration of cortisone (compound E). Publication of these observations was withheld until 1944, because extension of the experiments was not possible with the available supplies of cortisone. Protection against transplanted leukemia in rats by the administration of adrenal cortical hormones and ACTH was reported by Murphy and Sturm.[2] Dougherty and White[3, 4] demonstrated the depressing effect of ACTH on the circulating lymphocytes. Although Valentine, Craddock and Lawrence[5] in their own work were unable to demonstrate a clearcut relationship between the adrenal cortical hormone and the circulating lymphocytes, their paper contains an excellent review of the pertinent literature. Hills, Forsham and Finch[6] showed that, in the human, the administration of ACTH resulted in an increase in the circulating neutrophils and a decrease in the circulating lymphocytes and eosinophils. Because of this background of experimental work indicating a relationship between the adrenal cortex and the lymphatic and hematopoietic systems, the attention of hematologists and others interested in the study of the leukemias and related diseases was immediately focused on the possibility of using ACTH and cortisone in the treatment of these ailments.

Since the latter part of 1949, studies of the effectiveness of both ACTH and cortisone in the treatment of the leukemias and lymphomas have been in progress in several centres.[7] A number of reports have recently appeared which indicate that these hormones have a beneficial but temporary effect in diseases of this type in that they have caused some degree of abatement of the malignant process both in man[8–16] and in experimental animals.[17, 18]

ACTH was first used in the Hospital for Sick Children for the treatment of leukemia in a case of eosinophilic leukemia.[19] The temporary but apparently complete remission induced in this patient stimulated further investigations into the possibilities of this form of treatment.

The most important feature of this present study is further confirmation of that fact that remissions of an important degree can be induced in the leukemias and lymphomas of children by the administration of ACTH or cortisone. In almost every case some abatement of the malignant process was evident. In a significant number of patients the improvement was so dramatic that at the fastigium of the remission there was no clinical or laboratory evidence of leukemia. In no case was permanent benefit obtained. All patients in this series, except two, have relapsed and experience indicates that it is just a matter of time until these will show a recrudescence of their disease. An interesting observation, apparently more related to the fundamental nature of the individual case of leukemia than either the intensity or duration of the treatment, is the variation in the length of the induced relapse. The shortest complete remission lasted barely two weeks, the longest more than 12 weeks. The impression is that the leukemias with the low peripheral counts responded better than the so-called leukemic types. The series is, however, too small to formulate any definite opinion in this regard. Following the initial relapse all cases that have been retreated have shown a more sluggish response or have been almost entirely refractory to further hormonal treatment.

What is the fundamental nature of the leukemias and the lymphomas? Are they pri-

marily malignant diseases or are they due to a lack of some factor necessary for the proper development and maturation of the various white blood cells? It is generally considered that leukemia is a neoplastic process, peculiarly modified by the type of tissue involved. Most therapeutic agents hitherto employed in the treatment of leukemia have been noxious agents particularly lethal to cells in the process of multiplication. Their use has been directed toward the destruction of leukemia cells in the hope that a sufficient differential effect will be maintained so that the toxic action of these agents on the abnormal cell will be lethal and any deleterious effect on normal tissue will be minimal. In the rationale behind all such forms of treatment there is a tacit assumption that the process is neoplastic.

With ACTH and cortisone for the first time remissions in leukemia can be produced by steroids which are apparently normal products of the complex pattern of adrenal cortical activity. Although the administration of these hormones in the acute leukemias of children results in side effects which are evidence of either a distortion or over-activity of their normal physiologic function; in their action on the hemopoietic and lymphoid tissue, temporarily at least, they appear to supply or mediate the production of a substance necessary for normal activity.

Spontaneous remissions particularly following severe infections which have been noted in the past are probably the result of increased adrenal cortical function. The authors have seen a definite but incomplete clinical and hematologic remission following an appendectomy. Frequently, in the first few days after a child with leukemia is admitted to the hospital there is a change toward normal in the peripheral blood before any specific treatment is instituted. As this is a period in which the child is adjusting to a new environment and when numerous therapeutic and diagnostic procedures are employed. This temporary improvement in the blood picture might be explained on the basis of a stress reaction inducing some degree of increased adrenocortical activity.

It may be postulated that, as a part of the effect of the increased physiologic activity of the adrenal cortical steroids induced or supplied by the hormone therapy, a milieu is produced which is so unfavourable to the leukemic cells that they are destroyed. There is considerable evidence to support this concept. There is no flooding into the peripheral circulation of maturing or adult white cells proportional to the disappearance of the leukemic cells from the peripheral circulation, or bone marrow or in the decrease in the size of the lymph nodes, spleen and liver. Repeated marrow aspiration prior to and during the administration of the hormones indicate that there is a marked decrease in the total nucleated cell population of the marrow coincident with a decrease in the proportion of blasts and subsequently there is a reappearance of normal marrow constituents and a rise in the total nucleated count to normal. Chemical studies by Pearson et al.[8, 13] and the present authors' findings that the relative increase in excretion of uric acid and creatine appears to be proportional to the disappearance of the leukemic cells indicate a considerable break-down of leukemic tissue. Whatever the mechanism may be, there is considerable evidence, particularly in the early stages of the hormone therapy, that there is a massive dissolution of leukemic tissue.

From a therapeutic aspect, the disappointing feature of ACTH and cortisone therapy is the evanescent nature of the remission and the sluggish or refractory response to further treatment. This may indicate an antihormone effect. There is some clinical evidence to support this idea as the side effects of ACTH or cortisone therapy do not appear to be so marked during periods of retreatment. Chase[20] and Gordon[21] have ad-

duced experimental evidence that antihormones against purified adrenocorticotropic hormone can be demonstrated in the mouse and rat following administration of the hormone. However, if leukemia is fundamentally a neoplastic process it may be that after a shorter or longer period of time the leukemic cells become adapted to the altered environment with progress of the disease to its ultimate termination.

A more optimistic concept, which to date has little evidence to support it, is that the leukemias are not neoplastic processes but rather they represent a deficiency or block at some stage in development or maturation of the white blood cells. In an attempt to compensate for the deficiency of normal mature white cells, there is an outpouring of abnormal immature forms. To fit in with this hypothesis, the action of ACTH and cortisone may be explained by the assumption that at some stage in the complex metabolic change induced by the administration of these hormones, temporarily at least, a hypothetic maturation factor is supplied in sufficient quantities to initiate normal development of the white cells. Coincident with this there is an elimination and destruction of the unusable and imperfect immature cells.

In the present investigators' experience, in a case that responds well to ACTH or cortisone therapy, the following is the usual sequence of events in regard to the hematopoietic findings: decrease or disappearance of the circulating eosinophils, reduction or disappearance in number of blast forms in both peripheral blood and marrow, regeneration of the erythroid elements and finally reappearance of granulocytic cells and platelets. The latter may occasionally make an explosive appearance, increasing from 20,000 to over 200,000 within 24 hours.

An observation impossible to explain is the wide variation from case to case in the reaction to the hormones, both in regard to side effects and hematologic response. Dosage in the individual case was in main based upon the eosinophilic response. An attempt was made during treatment to adjust the dosage at a level which maintained the peripheral circulation free of eosinophils. In those children who initially showed only one or two eosinophils/cmm., this criterion was obviously of little use. The side effects in most children were relatively unimportant and were apparently tolerated well. As most of the leukemias were of the stem cell type simply designated as acute leukemia, it was not possible to correlate the character of response to treatment with any particular type of leukemia.

In the reaction following the first flush of enthusiasm for this new method of approach to the leukemia problems, one is apt to minimize the advance that has been achieved. There is little doubt that in the leukemias of children, with the administration of ACTH or cortisone, more complete hematologic and clinical remission can be obtained in a higher percentage of patients and with less toxic effects than with any other therapeutic agents thus far employed. Although the temporary nature of the remission is disappointing, an invaluable tool has been added to the armamentarium of the investigator.

Summary and Conclusions

The data concerning 16 cases of leukemia and one case of lymphosarcoma in children treated with pituitary adrenocorticotropic hormone (ACTH) and 11-dehydro-17-hydroxy corticosterone (cortisone) are presented.

Treatment of this group of diseases in children with these hormones resulted in complete but temporary remissions in a large proportion of the cases. Most patients in which

remissions were produced were almost completely refractory to retreatment with the hormones. Chemical studies indicated that in those patients in which a remission was produced, coincident with the remission there was a mass destruction of leukemic tissue.

Great variations were noted from patient to patient and also in the same patient in regard to the cytologic, physiologic and biochemical effects of the hormones.

Although ACTH and cortisone are unsatisfactory for permanent treatment of the leukemias and lymphomas, they offer invaluable tools for the investigator in the study of these diseases.

ACKNOWLEDGMENT

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SPANISH ABSTRACT

Tratamiento de las Leucemias y Linfosarcomas en Niños con la Hormona Adrenocorticotropica (ACTH) y el 11-dehydro-17-Hydroxy Corticosterone (Cortisone)

Los autores reportan los resultados obtenidos en 16 miños con leucemia y uno con linfosarcoma, tratados con ACTH o Cortisone. Trece pacientes fueron inicialmente tratados con ACTH y cuatro con Cortisone. Se observó una remisión hematologica completa de 3 a 13 semanas de duración en mas de 50% de los pacientes. Sin embargo, la mayoria de los pacientes que recibieron un segundo curso de hormonas, fueron parcialmente o totalmente refractarios al tratamiento. No se observó relación directa entre la retención de sodio o de potasio y la eficacia del tratamiento, pero si se observó cierta relación entre el aumento en la excreción de los 17-ketosteroides y la presencia de una remisión satisfactoria.

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EFFECTS OF ACTH AND CORTISONE ON LEUKEMIA IN CHILDHOOD

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THE rationale for the treatment of leukemia with ACTH and cortisone stems from previous investigations which demonstrated the effects of these agents on normal lymphatic tissue and lymphoid tumors. These studies, performed at a time when adrenocortical and pituitary adrenocorticotropic hormones were available only in minute amounts, provided a firm foundation for future work to be performed when the hormones were more readily obtainable.

Dougherty and White[1,2] in 1943 and 1944 reported observations which demonstrated that adrenocorticotropic hormones produced a lowering of circulating lymphocytes and involution of normal lymphoid masses in the rat. In 1944 Heilman and Kendall[3] observed regression of lymphoid tumors in mice following the administration of compound E, and Murphy and Sturm[4] noted a sharp reduction in the incidence of transplanted leukemia in a susceptible strain of rats following the administration of ACTH and of adrenocortical extracts. In 1948 Hills, Forsham and Finch[5] extended the investigations to humans and demonstrated that ACTH administration produced a sharp drop in circulating eosinophils and lymphocytes, and a rise in circulating neutrophils. Hellman[6] in March 1949 reported on the effect of ACTH in human chronic lymphatic leukemia.

With the increased availability of the hormones in the past year several reports have appeared which demonstrate the striking, though usually temporary, effects of ACTH and cortisone in certain cases of leukemia and lymphomas.[7-23]

It is the purpose of this paper to present observations on the treatment of 14 children with various types of leukemia with ACTH and cortisone. In this group, which consisted of successive cases, totally unselected, were 12 boys and 2 girls. One patient was 16 years of age, the others ranged from 2 to 12 years. The diagnosis was made by history, physical examination and study of peripheral blood and bone marrow, the latter obtained by aspiration from iliac crest or spinous process in most instances.

In the classification of the leukemias attention was directed to the predominant cell type in the marrow and to the presence or absence of cell differentiation along a particular line of development. In the cases where the predominant cell was the blast form and where no significant differentiation was discernible, it was not possible to detect morphologic characteristics which allowed definite classification into lymphocytic and granulocytic types. These cases were classified, therefore, merely as "acute leukemia." In cases where differentiation was evident the cell series involved was noted in the classification, the terms

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"acute," "subacute" and "chronic" indicating the degree of differentiation from immature to mature forms. Cases classified as leukemic lymphoma were those in whom lymph node biopsy established a diagnosis of lymphosarcoma at a time when blood and marrow were normal, but who, at a later date, exhibited progressive invasion of blood and marrow by blasts. On the basis of this classification nine cases were designated as acute leukemia, one each as acute monocytoid granulocytic, subacute granulocytic, and chronic granulocytic leukemia, and two as leukemic lymphoma (table 1).*

The therapy with either ACTH or cortisone was determined in most instances by the drug available. ACTH and cortisone were each used as initial therapy in seven cases. As

TABLE 1

SUMMARY OF RESULTS ACCORDING TO TYPE OF LEUKEMIA AND DEMONSTRATING APPARENT RELATIONSHIP TO PREVIOUS THERAPY

Type of Leukemia	No. of Patients	Response		
		None	Partial	Complete
Acute	9	1	2	6
Acute monocytoid granulocytic	1	1	—	—
Subacute granulocytic	1	1	—	—
Chronic granulocytic	1	1	—	—
Leukemic lymphoma	2	2	—	—
Total	14	6	2	6
Previously treated	7	4	2	1

the study of each patient progressed, however, various changes and combinations were instituted as described below. Both drugs were administered in four divided doses daily. ACTH therapy was usually begun with 60 mg./day for three days, followed by 40 mg./day thereafter. With cortisone, 100 mg./day were usually administered. Complete blood counts were performed every other day during hormone therapy. Marrow aspirations were performed weekly. Sodium, potassium, carbon dioxide combining power, and glucose determinations were performed on blood twice weekly. After discharge of a patient from the hospital, blood counts and marrow aspirations were performed at one to two week intervals.

A complete remission was considered to have occurred when there was (a) disappearance of all symptoms and signs of leukemia, including complete regression of previously recognized organ involvement, (b) return to normality of all cellular elements in the peripheral blood and (c) reduction in the percentage of blasts in the marrow to 4% or less and reappearance of erythropoietic elements. A partial remission consisted of significant symptomatic improvement and a definite change in the hematologic status in the direction of normality.

RESULTS

Table 1 summarizes the results of therapy based on the type of leukemia and demon-

* The nomenclature here employed is, for the most part, that recommended by a committee sponsored by the American Society of Clinical Pathologists and the American Medical Association, published in the Am. J. Clin. Path. 18:443, 1948.

strates the relationship to previous therapy. Six children with acute leukemia exhibited complete clinical and hematologic remissions. Two other children with acute leukemia exhibited partial remissions. The others, namely, one case of acute leukemia and the cases of acute monocytoid granulocytic, subacute granulocytic and chronic granulocytic leukemia, and leukemic lymphoma derived no benefit whatever. Of the eight children who demonstrated remissions two had received previous therapy (one with folic acid antagonists and one with radiation). Of the six children who failed to respond four had received previous antileukemic therapy.

In those children who responded favorably to therapy the clinical improvement was rapid and dramatic. Striking improvement in appetite, activity and general well being was evident. The appetite was frequently voracious and the children gained weight rapidly. Improvement in appetite could not, however, be interpreted as evidence of a remission since it was also observed to some extent in cases in which the leukemia failed to respond to hormone therapy. Bone pain, present in two of the patients (G. D., B. C.), disappeared after two days of therapy. Purpuric manifestations in two patients (G. D., B. A.) also ceased in two days before any rise in thrombocytes was evident. Hematologically the first signs of improvement were a reduction in the numbers of blasts and lymphocytes in the peripheral blood and the appearance of increasing numbers of mature granulocytes. The appearance of these mature granulocytes was generally unaccompanied by conspicuous appearance of intermediate forms. In several cases the reduction in blasts and lymphocytes was more pronounced than the increase in granulocytes so that a temporary leukopenia developed. These initial hematologic changes were usually evident by the end of the first week. Seven of the children in whom remissions were observed demonstrated low white blood counts prior to therapy, and in these the total white cell count and differential formula became normal in 3 to 4 weeks. The eighth child demonstrated an initial leukocytosis, the total white cell count falling gradually during therapy but never, however, reaching normal levels. A rise in thrombocyte count, frequently sudden and striking, occurred in 4 to 18 days. Maximum reticulocyte response occurred in the second or third week, following which the red cell count and hemoglobin rose steadily to normal values. It was common for the red count and hemoglobin to fall for the first 2 or 3 weeks following the onset of hormone therapy, but in only three cases were transfusions required, and in these patients a reticulocytosis had already occurred. In the marrow the first evidence of improvement was the appearance of increased numbers of erythroid elements, this usually being evident in one week. Maximum marrow improvement occurred in 3 to 4 weeks.

Case Reports

Case 1: H. K., a 4½ yr. old boy, developed pallor, weight loss and a tendency to fatigue. He was referred to the Children's Hospital of Winnipeg, where a diagnosis of leukemia was made. He was admitted to Bellevue Hospital 2 mo. later, having received no prior therapy but transfusion.

On admission the patient was a thin, drawn, weak boy, unable to sit up for more than a few minutes. The liver was palpable 6 cm. below the right costal margin, the spleen 3 cm. below the left costal margin. Hgb. was 11.0 gm./100 cc., RBC 4.5 million/cmm., WBC 2.8 thousand/cmm. (polymorphonuclear leukocytes 66%, band forms 7%, lymphocytes 25%, blasts 2%), thrombocytes 20.0 thousand/cmm. Marrow aspiration revealed 70% blast forms (Fig. 1A). The patient was given ACTH 60 mg./day for 3 days, 40 mg./day for 9 days. Clinical improvement was rapid and the boy was ambulatory in 1 wk. RBC and Hgb. remained at normal levels, the thrombocytes returned to normal in 8 days and the WBC rose to normal values in 10 days. On the sixth day of therapy myelocytes appeared in the peripheral blood to the extent of 11%. These persisted for an additional

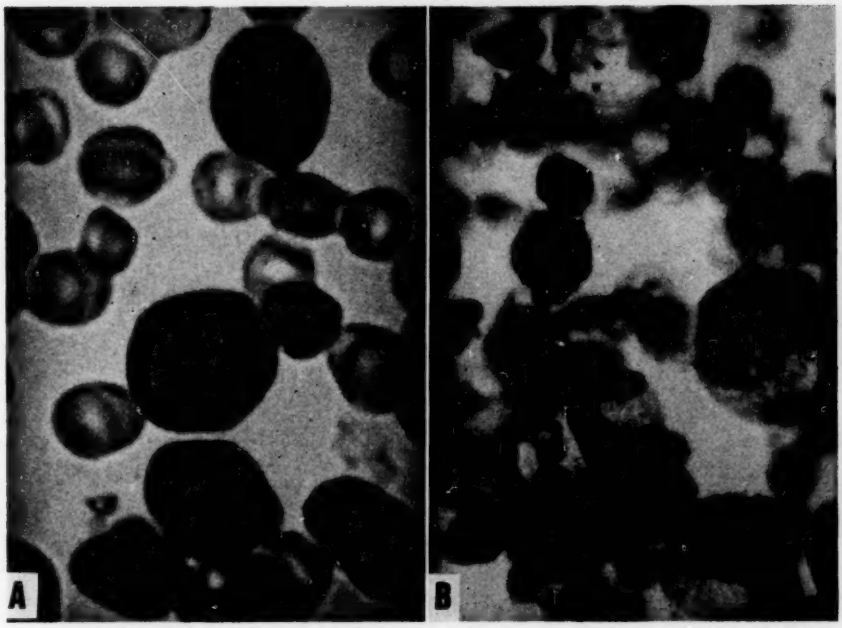

FIG. 1. Case 1 (H. K.). A. Marrow prior to therapy; blasts 70%. B. Marrow after 12 days of ACTH therapy; blasts 1%

4 days and were subsequently not evident. The differential formula became normal 2 wk. from the initiation of ACTH therapy. After 1 wk. of hormone therapy the blasts in the marrow had fallen to 4% and after 12 days to 1.5% (Fig. 1B). At this time the hepatosplenomegaly had almost completely receded. Therapy was discontinued at this time because of the occurrence of excess salt and water retention, muscular weakness, flattening of T waves on electrocardiogram, and a fall in serum potassium from 5.9 to 4.1 mEq./l. Diuresis occurred with discontinuance of hormone therapy; ECG and serum potassium returned to normal. With no further therapy the child remained in complete clinical and hematologic remission for an additional 17 wk. By 6 mo. after admission, however, the marrow again disclosed 60% blasts, and in another week 100%. At this point the patient began to exhibit pallor and weight loss, and he was readmitted to the Children's Hospital of Winnipeg.*

Hgb. was 13.7 gm./100 cc., WBC 41.9 thousand/cmm. (disintegrated cells 43.5%, blasts 8.0%, prolymphocytes 36.5%). ACTH therapy was begun and the child received 720 mg. over a period of 9 days. At the time of completion of therapy WBC had fallen to 2.9 thousand/cmm., but blasts were still evident in the peripheral blood. Hgb. had fallen to 7.4 gm./100 cc. and transfusion was necessary. Marrow aspiration at this time revealed some improvement, with a rise in erythroid elements to 23.4% and a fall in leukemic cells to 52%. Clinical improvement, however, was minimal and the child remained listless and anorexic.

Within a week following completion of ACTH therapy the marrow had reverted to the pretreatment state, and 2 wk. later WBC had risen to 81.0 thousand/cmm. The next day cortisone therapy was instituted, 50 mg./day for 13 days. During the 1st 5 days of cortisone therapy the WBC rose to 137.0 thousand/cmm. but subsequently fell steadily to 6.8 thousand/cmm. in 24 days at which time cortisone was discontinued. Clinical improvement during this course was again negligible.

WBC began to rise immediately after cessation of cortisone therapy and in 3 wk. was again 82.0 thousand/cmm. The patient developed a severe oral hemorrhage and cutaneous ecchymoses and

* For the subsequent notes on his course the authors are indebted to Drs. Bruce Chown and Jan Hoogstraten.

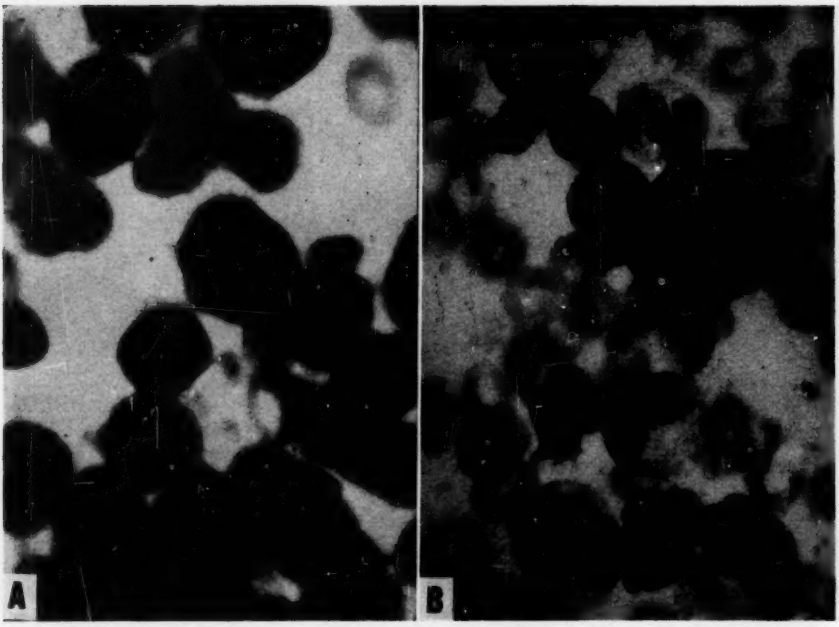

FIG. 2. Case 2 (B. C.). A. Marrow prior to therapy; blasts 98%. B. Marrow 4 wk. after initiation of ACTH therapy; blasts 2%.

required multiple transfusions. He received an additional 1000 mg. of cortisone for 4 days with no effect. He continued to exhibit hemorrhagic manifestations, progressive hepatosplenomegaly and anemia and died 16 days later.

This child differed strikingly from the other cases of acute leukemia observed in the series. He was the only patient who exhibited a granulocytic preponderance in the peripheral blood prior to therapy and the only one in whom immature granulocytes appeared during the occurrence of remission. On the basis of these facts he was originally classified as acute granulocytic leukemia. With relapse, however, immature lymphocytes appeared in the peripheral blood and extensive studies by Dr. Jan Hoogstraton of Winnipeg demonstrated that the predominant cells were of lymphatic origin. In the absence of any satisfactory explanation the case was included among those classified merely as acute leukemia.

Case 2: B. C., a 3½ yr. old boy, was admitted to Bellevue Hospital with a 4 wk. history of anorexia, pallor, listlessness and pain in the right hip. Admission physical examination was normal except for pallor of the skin and mucous membranes. Hgb. was 7.0 gm./100 cc., RBC 2.8 million/cmm., WBC 5.0 thousand/cmm. (lymphocytes 82%, granulocytes 10%, blasts 8%). Marrow revealed 98% blasts (Fig. 2A). Two days after admission, ACTH therapy was initiated, 60 mg./day for 3 days, followed by 40 mg./day for 11 days. Bone pain disappeared in 2 days and the general clinical condition improved rapidly. RBC and Hgb. fell during the 1st 2 wk., but following a reticulocytosis rose steadily to normal values. WBC remained fairly stationary for 3 wk., then rose steadily. The granulocytes, however, rose rapidly, a crossing of the lymphocytic and granulocytic elements occurring in the second week. In the marrow the blasts fell to 65% at the end of the first week, and by the fourth week had fallen to 2%, the remainder of the marrow differential being entirely normal (Fig. 2B).

In this child an attempt was made to study the effect of administration of small maintenance doses of ACTH. Therefore, at the completion of the 14 day course, ACTH, 10 mg. once a day, was instituted. However, 4 wk. after the introduction of maintenance therapy hematologic relapse became

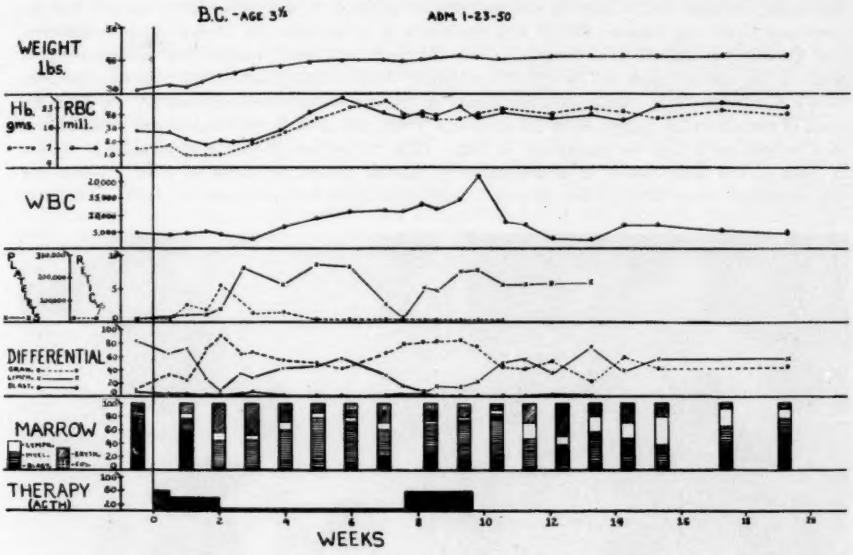

CHART 1. Case 2 (B. C.). Hematologic changes during 1st 20 wk. following onset of ACTH therapy.

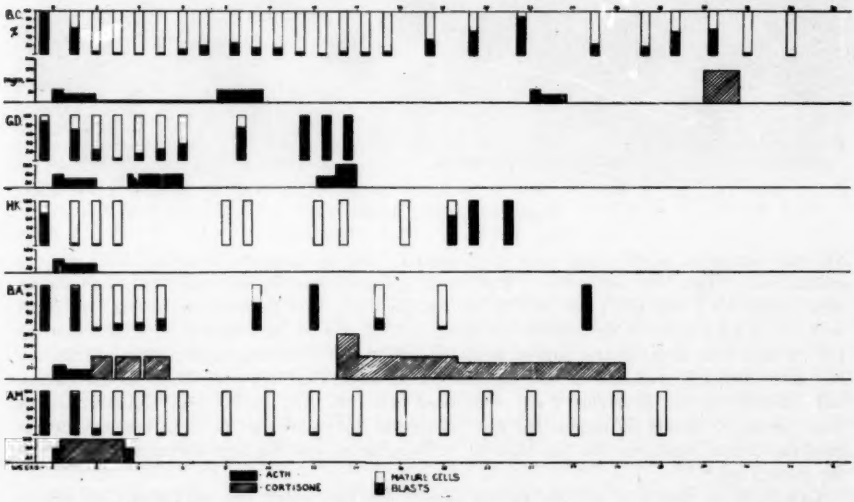

CHART 2. Relationship of hormone therapy to cellular composition of marrow in 5 patients who exhibited most complete responses. Shaded portions of bars indicate blasts, unshaded portions mature cells.

evident with increasing numbers of blasts in the marrow and peripheral blood, recrossing of the differential formula, and a drop in thrombocytes. In addition a 10% eosinophilia appeared in the peripheral blood and marrow. ACTH was then raised to 60 mg./day for 14 days. The thrombocytes rose, granulocytes again became predominant in the peripheral blood, eosinophilia disappeared, and blasts in the marrow again fell to 4%. The response to the second course of therapy was, however, slower than to the first, maximum improvement in the marrow not occurring until 5 wk. from the onset of the increased dosage. After an additional 5 wk., reversion of the marrow was again evident with progressive rise in the percentage of blasts. (The 1st 20 wk. of this child's course are shown in chart 1. The later course, as demonstrated by marrow change, is shown in chart 2.) The boy was readmitted 6 mo. after his first admission because the blasts in the marrow had increased to 88%.

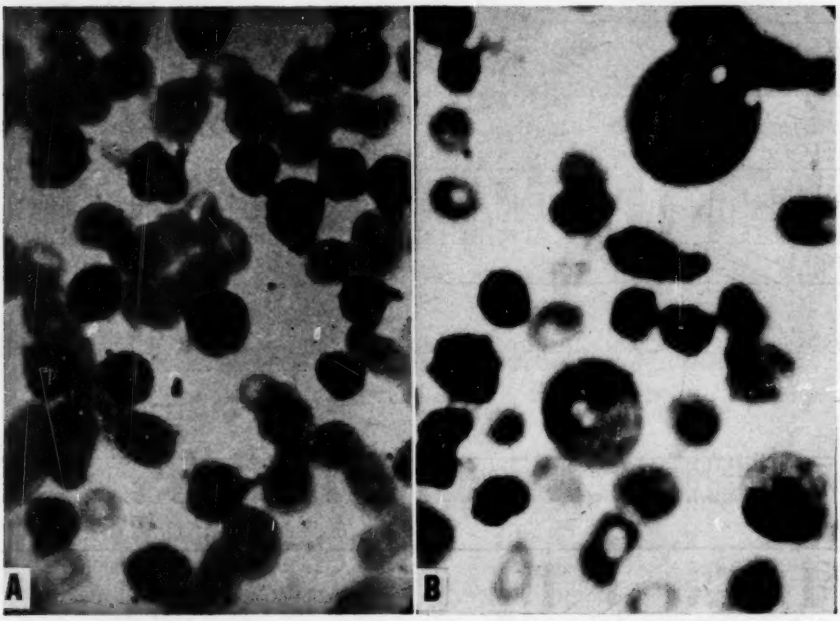

FIG. 3. Case (B. A.). A. Marrow prior to hormone therapy; blasts 98%. B. Marrow 2 wk. after beginning ACTH; blasts 6%.

The only symptoms at this time were slight anorexia and an occasional headache. RBC was 5.7 million/cmm., Hgb. 14.0 gm./100 cc., WBC 6.78 thousand/cmm. (lymphocytes 50%, granulocytes 49%, blasts 1%). He was given ACTH, 60 mg./day for 3 days followed by 40 mg./day for 8 days. In 24 days, blasts in the marrow had fallen to 27% and 15 days later to 20%. However, 11 and 23 days later, blasts in the marrow were again 53% and 57%, respectively. Cortisone therapy was then instituted at dosage of 150 mg./day for 11 days. Ten days later, blasts in the marrow had fallen to 4% and in another 2 wk. were found to be 2%. RBC, WBC, Hgb. and thrombocytes were normal. It should be emphasized that during this 36 wk. course the child has remained in excellent clinical condition. He has required no transfusions and has been ambulatory for almost the entire 9 mo.

Case 3: B. A., an 8½ yr. old boy, became ill with anorexia, weight loss and pallor. Two months later a 6 yr. old sister developed a persistent swelling of the left side of the neck. The 2 children were taken to the Ochsner Clinic in New Orleans, where a diagnosis of leukemia was made in both. They were treated with 4-amino pteroyl glutamic acid (aminopterin), but the sister failed to respond and died in 6 wk. The boy, however, made a good response and remained on intermittent antifolic acid therapy for the next year, with frequent interruptions due to the development of

oral mucous membrane ulceration. One year after the first signs of his original illness, he was considered to be resistant to folic acid antagonists and was transferred to Bellevue Hospital for hormone therapy.

On admission he was a thin pale boy. There were several crusted ulcerations on his lips, generalized lymphadenopathy, slight hepatosplenomegaly, and ecchymoses over his left eye and on both legs. Admission Hgb. was 9.5 gm./100 cc., RBC 2.4 million/cmm., WBC 5.4 thousand/cmm. (lymphocytes 48%, polymorphonuclear leukocytes 1%, eosinophils 2%, blasts 38%), thrombocytes 10,000/cmm. Marrow aspiration disclosed 98% blasts (Fig. 3A). ACTH therapy was begun with 60 mg./day for 3 days, then 40 mg./day for the succeeding 12 days. Clinical improvement was striking. Blasts disappeared from the peripheral blood and thrombocytes rose to 100,000/cmm. in the first week. Blasts in the marrow were 95% at the end of the first week, and 4% after 2 wk.

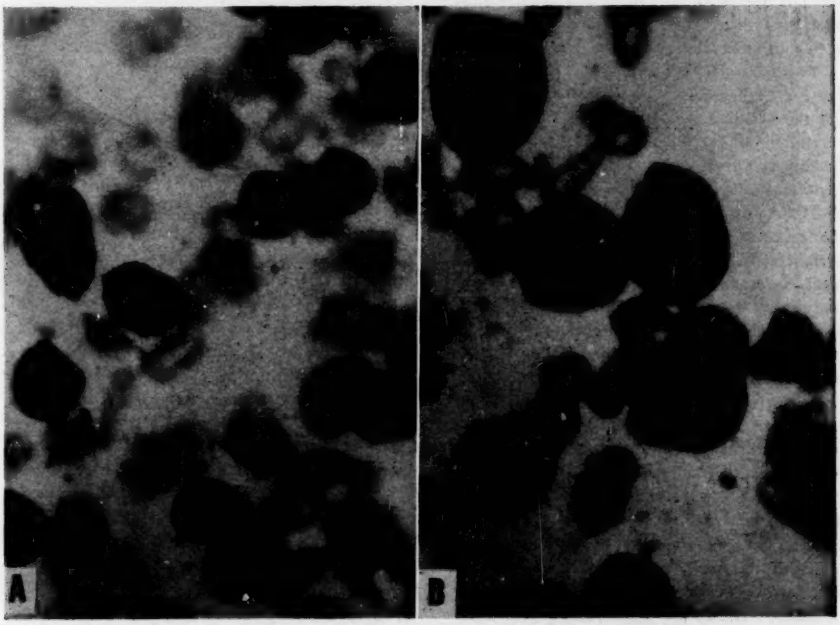

FIG. 4. Case 4 (G. D.). A. Marrow prior to hormone therapy; blasts 88%. B. Marrow 3 wk. after initiation of ACTH therapy; blasts 4%.

on ACTH therapy (Fig. 3B). During the 1st 2 wk. RBC and Hgb. fell steadily to levels of 1.5 million/cmm. and 5.5 gm./100 cc., respectively. On the tenth day however, a reticulocytosis of 5% was evident. At this time the patient was given 2 transfusions, following which the RBC and Hgb. showed a steady rise to normal values. During the same 2 wk. period the WBC also fell, so that after 14 days the total leukocyte count was only 800/cmm. At this point cortisone therapy was substituted for ACTH at dosage levels of 100 mg./day for 19 days. On this therapy clinical improvement persisted, and the RBC, WBC and Hgb. rose to normal values. However, the weekly marrow aspirations revealed progressive increase in the number of blasts, so that at the end of the 19 days of cortisone therapy, and 5 wk. after institution of hormone therapy, blasts were again 25% of the marrow differential. The boy was discharged under the care of Dr. Charles Gillespie of Laurel, Miss. During the following month, although clinical well-being persisted, marrow reversion progressed, so that by the 35th day there were 100% blasts in marrow aspiration and 40% in peripheral blood. Eight days later cortisone therapy was again instituted with dosage of 200 mg./day for 7 days, 100 mg./day for 37 days and 75 mg./day for the remaining 57 days of life. Within 20 days the blasts had fallen to 25% and 12 days later were 3%. The spleen, which had been enlarged to

10 cm. below the left costal margin at the onset of this course of therapy, became nonpalpable and the child was in excellent clinical condition. Despite continuing therapy, however, this remission was only short-lived. Blasts began to reappear in the peripheral blood and marrow, and in 6 wk. his WBC had risen rapidly to 106.5 thousand/cmm. with 75% blasts in the peripheral blood. Uncontrollable bleeding from the nose and intestinal tract developed, and the boy died 13 days later.

Case 4: G. D., a 7 yr. old boy previously well, developed pallor, easy bruising and recurrent epistaxis. He was admitted to St. Vincent's Hospital, Indianapolis, where a diagnosis of leukemia was made. He received no therapy other than transfusions, and was transferred to Bellevue Hospital 5 mo. later.

On admission the patient was a thin, chronically ill child. The gums were hypertrophied, spongy and bled easily. There was a generalized lymphadenopathy, but no splenomegaly. The right wrist and left heel were painful, tender and swollen. On admission the RBC was 6.6 million/cmm., Hgb. 17.4 gm./100 cc., WBC 1.9 thousand/cmm. (lymphocytes 60%, prolymphocytes 18%, granulocytes 22%), thrombocytes 10.0/cmm. The marrow revealed 88% blasts (Fig. 4A).

Two days after admission ACTH therapy was begun, 60 mg./day for 3 days followed by 40 mg./day for 11 days. Clinical improvement was rapid. Bone and joint pains disappeared in 2 days, as did the bleeding from the gums. The patient became active and cheerful and was ambulatory after several days. The RBC and Hgb. fell during the 1st 12 days, but following a reticulocytosis rose steadily to normal values. The WBC fell to 850 thousand/cmm. during the first week, then rose steadily to normal values. A sharp rise in thrombocyte count occurred on the tenth day. Blasts in the marrow fell to 25% during the 2 wk. of therapy and continued to fall to 4% by the end of the week following the cessation of ACTH administration (Fig. 4B). At this time, however, lymphocytes in the peripheral blood had again risen to 71%. Because of this, and despite the striking marrow improvement, a second course of ACTH, 60 mg./day for 19 days, was instituted. Throughout this period the clinical improvement continued, RBC and Hgb. continued to rise, and thrombocyte count and WBC remained normal. However, examination of the marrow at weekly intervals disclosed evidence of progressive relapse, the percentage of blasts rising from 4% at the onset to 26% at the completion of the second course of therapy. After 53 days the child was returned home for further care under the observation of Dr. Paul J. Fouts and Dr. Harold Stadler of Indianapolis. Two weeks later marrow aspiration revealed 75% blasts, although the child was clinically well. Within 17 days the boy had developed a tendency to fatigue, anorexia, splenomegaly and generalized lymphadenopathy. He was admitted to St. Vincent's Hospital, Indianapolis, where his RBC was found to be 3.61 million/cmm., Hgb. 10 gm./100 cc., WBC 3.3 thousand/cmm., with 25% blasts in the peripheral blood, 100% in the marrow. He was given ACTH, 50 mg./day for 7 days and 100 mg./day for the next 7 days. There was no clinical response, and the WBC rose from 3,300 to 54,000/cmm. with 90% blasts in the peripheral blood. Ten days later, 4-amino-N-methyl folic acid (a-methopterin), 5 mg./day, was begun and within 24 days an excellent remission had been achieved.

Case 5: A. M., a 2 yr. old girl, became ill with symptoms of an upper respiratory infection. Investigation because of persistent anorexia and developing pallor disclosed acute leukemia, and the patient was admitted to Bellevue Hospital.

On admission the child was pale, listless and irritable. Her eyelids were edematous and her face puffy. The remainder of the physical examination was negative. RBC was 3.48 million/cmm., Hgb. 10.5 gm./100 cc., WBC 4.6 thousand/cmm. (polymorphonuclear leukocytes 5%, lymphocytes 53%, prolymphocytes 34%, blasts 7%), thrombocyte count 90,000/cmm. Marrow aspiration revealed 100% blasts (Fig. 5A).

The patient was given ACTH therapy, 60 mg./day, but after 2 days developed giant urticaria. Therefore, therapy was changed to cortisone, 100 mg./day for 21 days with no reaction and gradual clearing of the urticaria. At the completion of cortisone therapy, ACTH was again administered, 60 mg./day for 2 days, but no urticaria reappeared.

On therapy the WBC fell to 1.6 thousand/cmm. during the first week, but then rose steadily to normal. Blasts disappeared from the peripheral blood in the first week and platelets returned to normal level during the second week. RBC and Hgb. fell during the 1st 3 wk. of therapy, but following a reticulocytosis rose spontaneously to normal values. Two weeks after onset of therapy blasts in the marrow had fallen to 16%, at 3 wk. they were 7%, and at 4 wk. 2% (Fig. 5B). By this time the child was in excellent clinical condition, active and ambulatory.

Marrow and peripheral blood studies have been performed on this patient every 2 wk. since the

completion of therapy. She remains in complete clinical and hematologic remission 33 wk. from the onset of hormone therapy.

Case 6: J. C., a 4 yr. old boy, became ill with unexplained fever and anorexia which persisted for 1 wk. A blood count at that time suggested leukemia, and the diagnosis was confirmed by bone marrow aspiration. In the next 4 mo. he exhibited progressive anorexia, weight loss, generalized lymphadenopathy, hepatosplenomegaly, and many episodes of epistaxis, requiring several transfusions. He was transferred to University Hospital.

On admission the patient was an emaciated, pale boy appearing both acutely and chronically ill. There were numerous petechial and ecchymotic areas over the trunk and extremities. The liver was palpable 9 cm. below the right costal margin, the spleen 6 cm. below the left costal margin, and

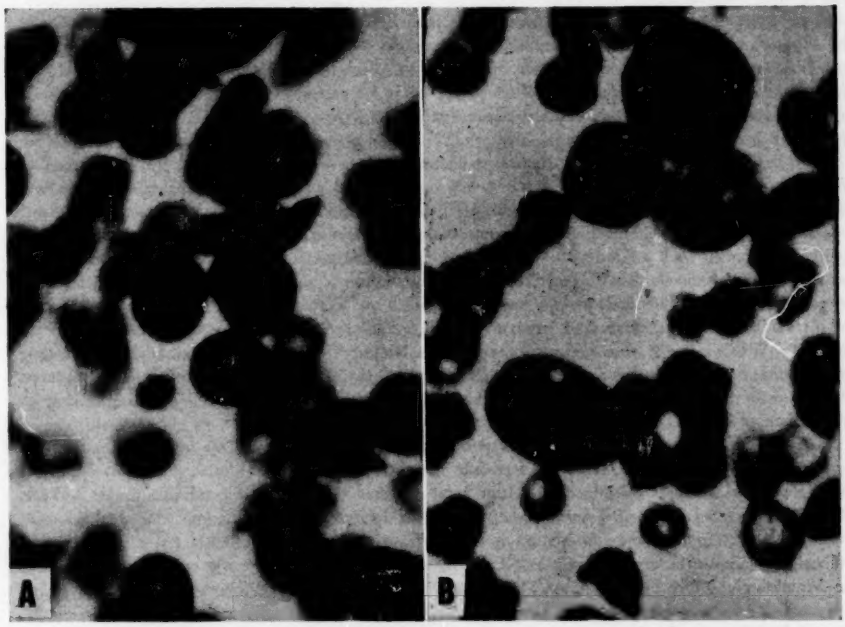

FIG. 5. (A. M.). A. Marrow prior to hormone therapy; blasts 100%. B. Marrow 4 wk. after initiation of hormone therapy; blasts 2%.

there was generalized lymphadenopathy. Hgb. was 8.0 gm./100 cc., RBC 2.8 million/cmm., WBC 34.0 thousand/cmm., platelets 8,000/cmm. There were 86% blasts in the peripheral blood, 95% in marrow.

The patient was given cortisone 100 mg./day for 7 days and 160 mg./day for the following 7 days. There was no clinical or hematologic improvement on therapy. The patient continued to have repeated, massive epistaxis, and required multiple transfusions. On the 14th hospital day he had a sudden, massive, gastrointestinal hemorrhage and died.

Case 7: J. D., a 6 yr. old boy, became ill with symptoms of a mild upper respiratory infection. Because of a persistent fever he was hospitalized, and a diagnosis of leukemia was established. The child received aminopterin 1 mg./day for 32 days and then again, after a period of 10 days, for 9 days. Because of the development of severe leucopenia he was transferred to University Hospital.

On admission the patient was a pale, chronically ill boy. There was marked redness and swelling of the upper and lower lids of the right eye, numerous hemorrhagic ulcerations of the buccal mucous membranes, and hepatosplenomegaly. RBC was 2.52 million/cmm., Hgb. 7.5 gm./100 cc., WBC 1.0 thousand/cmm., with 50% blast forms in the differential formula. The marrow revealed

70% blast forms and 20% of large cells with large, irregular, finely reticulated nuclei and blue-gray, finely granular and often vacuolated, cytoplasm. This was considered to be a case of acute monocytoid granulocytic leukemia.

Cortisone, in doses of 100 mg./day, was begun on admission. This was increased to 200 mg./day on the 5th day and to 300 mg./day on the 17th day, a total of 3700 mg. being given over a 20 day period. Apart from a slight improvement in appetite there was no evidence of clinical improvement. WBC fell to 850/cmm., RBC to 1.66 million/cmm., Hgb. to 4.6 gm./100 cc. A large ulcer developed on the right lower eyelid, and culture of the exudate disclosed B. pyocyaneus. Despite massive and varied antibiotic therapy, the lid became gangrenous. Hormone therapy was discontinued on the 18th hospital day and transfusions were given. The patient's condition became worse rapidly, and he died 1 wk. later.

Case 8: J. Co., a 10 yr. old boy, was admitted to Bellevue Hospital because of the development of a mass of enlarged nodes in the left supraclavicular region. The child had no complaints, and physical examination revealed a cluster of large, firm, nontender nodes in the left supraclavicular fossa as the only abnormal finding. Before biopsy could be performed, the child developed varicella and was transferred to a communicable disease hospital. When he returned 2 wk. later, the mass of nodes had shrunken markedly in size, and 2 lymph node biopsies were reported as showing "hyperplasia." Blood and marrow studies at that time were normal. The child was discharged to follow-up clinic, and was well for 5 mo. when he presented with acute dyspnea, pleural effusion, widening of the mediastinum and generalized lymphadenopathy. Lymph node biopsy at this time revealed lymphosarcoma. Peripheral blood and marrow studies again revealed no abnormalities. The patient responded well to radiation therapy and was discharged to radiation outpatient clinic. He was readmitted 2 mo. later with fever, cough, reaccumulation of right pleural effusion, hepatosplenomegaly, generalized lymphadenopathy, and a large, firm, nontender mass on the back. At this admission WBC was 9.0 thousand/cmm. with 65% granulocytes and 25% lymphocytes. Two weeks later the WBC was 5.5 thousand/cmm. with 75% lymphocytes. Marrow examination at this time disclosed almost complete replacement by lymphoblasts. A 2 wk. course of aminopterin produced regression of the hepatosplenomegaly, but did not alter the marrow findings. WBC rose steadily to 120.0 thousand/cmm., with increasing numbers of blasts.

Three months later ACTH became available and the boy was given 60 mg./day for 3 days, and 40 mg./day for 5 days. Therapy was then discontinued because of the development of excess fluid retention and hypokalemia. The serum potassium had fallen from 6.2 mEq./l. to 3.8 mEq./l. The ECG revealed flattened T waves, and the patient demonstrated marked muscular weakness. On cessation of therapy and the administration of potassium chloride by mouth, the patient lost 2.3 kg. in weight, and the serum potassium and ECG returned to normal. There was no significant clinical or hematologic improvement on ACTH therapy. Three days later cortisone, 100 mg./day, was initiated. There was no clinical or hematologic improvement in 8 days, and the drug was discontinued. Death occurred 4 days later.

Case 9: A.B., a 3½ yr. old boy, became ill with fever, chest pain and dyspnea. He was admitted to a local hospital where a diagnosis of "pleurisy" was made and a rib resection and drainage performed. Following surgery, however, chest roentgenographic examination revealed a widened mediastinum, and a biopsy of a large superficial lymph node revealed lymphosarcoma. Peripheral blood and bone marrow at this time were considered normal. The patient received radiation therapy with some clinical improvement, but in the next 2 mo. hematologic investigation demonstrated progressive infiltration of blast forms in the marrow and also their appearance in the peripheral blood. The child was transferred to Bellevue Hospital.

On admission the patient was pale, weak and dyspneic. There was marked facial edema, generalized lymphadenopathy, a large left pleural effusion and hepatomegaly. WBC was 25.0 thousand/cmm. with 70% blast forms in the peripheral blood and 95% in the marrow. The patient was given cortisone, 100 mg./day, but exhibited no clinical or hematologic effect, and died after 7 days of therapy.

Case 10: D.F., a 3½ yr. old boy was admitted to Bellevue Hospital with a 6 wk. history of listlessness, anorexia and easy bruising.

On admission the patient was a pale, thin boy who appeared chronically ill. There were numerous ecchymoses over the extremities, generalized lymphadenopathy, and hepatosplenomegaly. RBC was 3.75 million/cmm., Hgb. 9.0 gm./100 cc., WBC 129.0 thousand/cmm. (blasts 57%, metamyelocytes

14%, polymorphonuclear leucocytes 15.5%, lymphocytes 23.5%, normoblasts 2%). Marrow revealed blasts 77%, myelocytes 3.5%, metamyelocytes 4.5%, polymorphonuclear leukocytes 4.5%, lymphocytes 8.5%, normoblasts 5.5%. He was given 1460 mg. of ACTH in 21 days, but sustained no clinical improvement. WBC rose to 225.6/cmm. during hormone therapy. ACTH was discontinued and a-methopterin therapy was instituted. An excellent clinical and hematologic remission was evident in 2 wk.

Case 11: D.B., a 16 yr. old boy, was first hospitalized at Indiana University Hospital with a 6 mo. history of pains in the legs, weight loss and repeated epistaxis. Physical examination at that time revealed increased mediastinal dullness and splenomegaly. WBC was 360.0 thousand/cmm. (blasts 2%, myelocytes 8%, metamyelocytes 25%, bands 35%, polymorphonuclear leukocytes 19%, eosinophils 15%, basophils 3%, lymphocytes 3%). He received blood transfusions and roentgen therapy, and 8 mo. later he was begun on ethylcarbamate (urethane) therapy with gradually increasing dosage to 3.0 gm./day. On urethane he exhibited some symptomatic improvement and a fall in WBC to levels ranging from 6.0 to 82.0 thousand/cmm. He remained on urethane for 13 mo. and 1 mo. later was sent to New York for hormone therapy.

On admission the patient was a cachectic boy who appeared both acutely and chronically ill. The cervical and inguinal nodes were enlarged, and the spleen was palpable 10 cm. below the left costal margin. The extremities were markedly emaciated, and the right knee was swollen, painful and tender. Hgb. was 10.8 gm./100 cc., RBC 3.0 million/cmm., WBC 18.0 thousand/cmm. (blasts 19%, myelocytes 12%, polymorphonuclear leukocytes 56%, basophils 2%, lymphocytes 10%). The marrow revealed a striking predominance of myelocytes. The patient was begun on ACTH therapy, but died after 5 days, having received a total 360 mg.

Case 12: G.H., a 3 yr. old girl, became ill with anorexia, weight loss, weakness and pallor. A diagnosis of leukemia was made, and the child was given aminopterin intermittently for 1 mo., with frequent interruptions due to the occurrence of hemorrhagic manifestations. She was maintained on transfusions until transfer to University Hospital 5 mo. after illness began.

On admission she was a thin, pale girl who exhibited marked wasting. There were scattered petechiae and ecchymoses over all extremities. The abdomen was markedly protuberant, and striking hepatosplenomegaly was evident. The spleen was enormous, extending to the symphysis pubis on the left and crossed the midline of the abdomen to extend into the right upper and lower quadrants. Roentgenographic studies disclosed osteolytic lesions of the humeri and ribs. Hgb. was 9.6 gm./100 cc., RBC 3.26 million/cmm., WBC 6.5 thousand/cmm. (blasts 25%, polymorphonuclear leukocytes 42%, lymphocytes 26%, monocytes 2%, eosinophils 1%). Marrow revealed 95% blast forms. The day after admission, the child was begun on cortisone therapy and received 4960 mg. over a period of 31 days. On therapy the appetite improved as did the child's general appearance and activity. The most striking clinical change was the rapid reduction in the size of the spleen. After 3 wk. of therapy this organ extended to but 9 cm. below the left costal margin, and had receded entirely from the right side of the abdomen. WBC rose steadily to 11.0 thousand/cmm., and the blasts disappeared from the peripheral blood after 16 days. After 2 wk. of cortisone therapy a marked improvement in the marrow was evident. Blasts had fallen to 10% and there was a striking increase in nucleated red cell forms. No change in the osteolytic bone lesions was evident. Less than 1 wk., after the completion of therapy the RBC and Hgb. had begun to fall, occasional blasts again appeared in the peripheral blood, and the child complained of severe pain in the extremities. In the following week the Hgb. fell precipitously to 5.0 gm./100 cc. and the WBC rose with extreme rapidity to 138.0 thousand/cmm. There was complete marrow relapse. The child was retreated with cortisone, but died after having received 1200 mg. over a period of 7 days.

Case 13: T. D., a 12 yr. old boy, became ill with a sudden onset of fever and dyspnea. Upon hospitalization, he was found to have an enlarged mediastinum, left pleural effusion and splenomegaly. Blood and bone marrow examinations revealed acute leukemia. The boy was treated with thoracentesis, radiation, antibiotics and transfusions with little effect, and he was transferred to University Hospital after 2 mo.

On admission the patient was an acutely ill, dyspneic and cyanotic boy. There was striking enlargement of the parotid area and a marked generalized lymphadenopathy. Chest examination indicated a left pleural effusion. The spleen was hard and extended to within 3 cm. of the symphysis pubis. The liver was palpable 6 cm. below the right costal margin, and there was pitting edema of both lower extremities. The blood pressure was 110/60 mm.Hg. Hgb. was 8.9/100 cc., WBC 2.9 million/

TABLE 2

SUMMARY OF CASE REPORTS

Case	Age (yr.)	Sex	Type of Leukemia	Duration of Illness Before Hormone Therapy (mo.)	Previous Therapy	Hormone Therapy Initial Course (mg./day)	Result of Initial Course	Retreatment (mg./day)	Result	Total Duration of Disease (mo.)
1. H.K.	4	M	Acute	2	0	ACTH 540/12	Complete remission, 17 wk.	ACTH 720/9	Moderate hematologic effect; slight clinical improvement.	11
								Cortisone 650/13	Moderate hematologic effect; slight clinical improvement.	
								Cortisone 1000/5	No effect; died.	
2. B.C.	3½	M	Acute	1	0	ACTH 620/14 ACTH 280/28	Complete remission; marrow relapse in 6 wk.	ACTH 840/14	Complete remission, 10 wk.	14+
								ACTH 500/11	Complete clinical, partial hematologic remission.	
								Cortisone 1650/11	Complete clinical and hematologic remission.	
3. B.A.	8½	M	Acute	12	Aminopterin A-methopterin	ACTH 620/14 Cortisone 1900/19	Complete remission, but bone marrow relapse beginning during third week of therapy and progressing despite change to cortisone.	Cortisone 9375/101 6 wk. after initial course.	Clinical and hematologic remission for 10 wk., then relapse and death despite continuing therapy.	21
4. G.D.	7	M	Acute	4	0	ACTH 620/14 ACTH 1140/19	Complete remission, but evidence of bone marrow relapse 1 wk. after completion of first course. Progression despite resumption of therapy.	ACTH 1600/14 6 wk. after initial course.	No response to ACTH. Remission following folic acid antagonist.	15+
5. A.M.	2	F	Acute	1	0	ACTH 120/2 Cortisone 2100/21 ACTH 120/2	Complete remission persisting 32 wk. after initial course.	—	—	12+
6. J.C.	4	M	Acute	4	0	Cortisone 1660/17	No response; died.	—	—	6
7. J.D.	3	M	Acute monocytoid Granulocytic	2	Aminopterin	Cortisone 3700/20	No response; died.	—	—	5
8. J. Co.	10	M	Leukemic Lymphoma	10	Radiation Aminopterin	ACTH 380/8 Cortisone 800/8	No response; died.	—	—	14
9. A.B.	3	M	Leukemic Lymphoma	2	Radiation	Cortisone 700/7	No response; died.	—	—	5
10. D.F.	3½	M	Subacute Granulocytic	1½	0	ACTH 1460/21	No response to ACTH. Remission after folic acid antagonist.	—	—	8+
11. D.B.	16	M	Chronic Granulocytic	22	Radiation Urethane	ACTH 360/5	No response; died in 5 days.	—	—	64
12. G.H.	3	F	Acute	4	Aminopterin	Cortisone 4960/31	Moderate improvement, relapse in 2. wk.	Cortisone 1200/7	No response; died.	
13. T.D.	12	M	Acute	1½	Radiation	Cortisone 6400/33	Slight clinical and hematologic improvement—rapid relapse and death.	—	Partial remission.	8
14. D.K.	2½	M	Acute	2	0	Cortisone 3000/25	Complete remission—5 wk.	—	Complete remission.	3

cmm., WBC 69.0 thousand/cmm., thrombocytes 90,000/cmm. There were 67% blasts in the peripheral blood and 95% in the marrow.

Thoracentesis was performed with the removal of 1500 cc. of fluid. Four days after admission cortisone therapy was instituted with 6400 mg. given over a period of 33 days. Dosage began with 80 mg./day, and was increased steadily to 300 mg./day for the last 2 wk. of therapy. A definite improvement in appetite and a sense of well-being resulted from the cortisone therapy. At the higher dosage levels there was some regression in the cervical nodes; the spleen edge receded 2.5 cm. in all palpable areas and was noted to be soft rather than stony hard. After 3 wk. of therapy the WBC had fallen to 15.0 thousand/cmm. and the blasts in the peripheral blood to 0 to 5%. The marrow, however, failed to show any improvement.

Shortly after the increase of cortisone to dosage levels of 300 mg./day, definite signs of toxicity began to appear. There was a rapid gain in weight from 35.4 kg. to 40.8 kg. Peripheral edema increased and ascites developed. The face became markedly rounded and developed a peculiar purplish-red, plethoric appearance which was in striking contrast to the pallor of the rest of the body and the low Hgb. and RBC values. After 10 days of 300 mg. of cortisone/day the blood pressure had risen to 160/90 mm.Hg. and the patient developed marked dyspnea, moist rales at the lung bases, and severe headache. Cortisone therapy was discontinued, and digitalis and mercurial diuretics were given. The child had a marked diuresis and lost 3.2 kg. in a single day. The signs of decompensation and the elevated blood pressure disappeared, but the plethoric facies remained evident. At this point the child became somewhat depressed. Further therapy consisted of ethyl carbamate (urethane) and radiation, but the patient failed to improve and died 4 mo. after admission.

Case 14: D. K., a 27 mo. old boy, was admitted to Bellevue Hospital with a 2 mo. history of bruising easily, accompanied by intermittent low grade fever, anorexia and irritability. However, 8 mo. previously swellings had appeared at the site of 2 injections. These were presumably hematomas. Four days before admission, his family physician noted generalized lymphadenopathy and marked anemia.

Examination on admission revealed pallor, lethargy, moderate generalized lymphadenopathy and a temperature of 40.5° C. Showers of petechiae were noted over the trunk and on the mucous membranes. The liver extended 2 cm. and the spleen 3 cm. below the costal margin. Hgb. at this time was 7 gm. and the WBC 3.9 thousand/cmm. Peripheral blood showed 2% blast forms, 88% lymphocytes and 10% granulocytes. Bone marrow revealed 65% blasts and 35% lymphocytes with rare erythroid elements.

On the second hospital day, cortisone therapy in doses of 150 mg./day was begun, and in the following 25 days he received a total of 3000 mg. Petechiae cleared rapidly and by the 7th hospital day the marrow showed only 16% blast forms. On this day he became acutely ill with high spiking temperature. Staph. aureus hemolyticus was recovered from numerous blood cultures. Intensive therapy with penicillin, aureomycin and chloromycetin was given over the following 14 days. Blood cultures were sterile after the eighth day of chemotherapy. During the period of sepsis, erythropoiesis was minimal and platelet counts remained low. Numerous transfusions were given. However by the 20th day of cortisone therapy there was evidence of active erythropoiesis and a good platelet response. By the 27th hospital day the marrow showed 33% normoblasts and 2% blast forms. At the time of his discharge on the 35th day of hospitalization, he showed evidence of complete clinical and hematologic remission.

A summary of the cases just presented is given in table 2.

Discussion

The results obtained in this series and those reported by other workers indicate that ACTH and cortisone possess striking effectiveness as antileukemic agents. The results in any series would, however, seem to depend on a combination of factors: the form of the leukemia, the duration of illness, the type of previous therapy, and the type, dose and duration of hormone therapy. The group herein presented has too few cases of each form of leukemia to permit any definite statement of responsiveness based on the type of the disease. However, of 10 cases of acute leukemia, 6 demonstrated striking clinical and hematologic improvement, two showed slight to moderate improvement and 2 complete

lack of response. One of the cases which failed to demonstrate any improvement was of the monocytoid (myelomonocytic) variety, and the resistance of this type has been noted by other workers. Pearson et al.,[15] Wintrobe et al.[17] and Reisner[22] mention a total of seven cases of monocytic or myelomonocytic leukemia all of whom failed to show any benefit from ACTH and cortisone therapy. One case in the present group originally classified as acute granulocytic leukemia demonstrated a prolonged remission but later observations indicated that this was probably lymphocytic; the cases of subacute and chronic granulocytic leukemia failed to respond to hormone therapy. Stickney[18] and Dameshek[21] also report poor results with granulocytic leukemias, the latter author expressing the opinion that the course of the granulocytic varieties may, in fact, be accelerated. Two cases of leukemic lymphoma also failed to evidence any improvement. Although the disease in these patients apparently began as lymphosarcoma, the state of the peripheral blood and marrow at the time of initiation of hormone therapy suggests that the differentiation between leukemic lymphoma and acute leukemia is an artificial one. Of five children with lymphosarcoma treated with ACTH by Farber et al.,[16] two showed temporary improvement and three failed to respond. It would appear, therefore, that the leukemias least likely to respond to hormone therapy are the monocytoid varieties and the granulocytic types which are differentiated beyond the blast stage.

With regard to the duration of illness prior to therapy, the three patients who exhibited the longest and most complete remissions (A.M., H.K., B.C.) had been ill for 3, 8 and 4 weeks, respectively, prior to hormone therapy. On the other hand, complete failure was encountered with Patient J.C. who had been ill for only 3 weeks, while excellent remissions were achieved in Patients B.A. and G.D. who have been ill for 10 and 4 months, respectively, prior to hormone treatment. All six patients had the acute form of leukemia. The patients who responded best exhibited the fewest symptoms and the least evidence of organ enlargement and hemorrhagic diathesis. Those who failed to benefit from hormone therapy were usually extremely ill prior to the initiation of ACTH or cortisone treatment. It appears, therefore, that the significant factor in determining the responsiveness to hormone therapy is not the duration of illness per se, but the extent to which the disease has progressed since its onset.

The relationship of previous therapy to response has been mentioned earlier. It is again the authors' impression that responsiveness is determined by the extent of the disease and the severity of illness rather than by the type and amount of previous therapy. An excellent response was obtained in one patient (B.A.) who had received folic acid antagonists intermittently for 10 months, and a moderate response was evident in another patient (G.H.) who had received antifolic acid therapy (aminopterin) for one month. None of the patients who had been treated with radiation derived any benefit from the hormones, but each was critically ill at the time ACTH or cortisone therapy was begun. The experience with Patients G.D. and D.F. also indicates that certain individuals who are refractory to hormone treatment may still respond to therapy with folic acid antagonists. The results in Case 2 (B.C.) suggest that some patients who are resistant to ACTH may still respond to cortisone. However, different doses of the two agents were employed, and the significance of this factor remains to be clarified. The authors have had no experience with treatment of cortisone-refractory cases with ACTH.

The doses of ACTH and cortisone in this series were chosen empirically and were not based upon determination of eosinophil levels or eosinophil response. The reason for this decision was that the eosinophil counts were frequently found to be zero or very low prior

to the initiation of hormone therapy. The relationship of therapy to the cellular composition of the marrow in the five patients who exhibited striking remissions is shown in figure 4. Continuation of hormone administration after 2 to 3 weeks appeared to have little influence on the ultimate response or on the occurrence of relapse. One patient (H.K.) who remained in complete remission for 17 weeks had received 12 days of ACTH therapy; another (A.M.) who remained in remission 33 weeks received treatment for 25 days. On the other hand, three patients (B.A., G.D., B.C.) exhibited marrow relapse while on continued therapy of 33, 33 and 42 days' duration, respectively. Due to the lack of proper control in the choice of the drug administered no statement can be made on the relative effectiveness of ACTH and cortisone. It is interesting to note that the patient who has had the longest remission in this series (A.M.) was treated with cortisone for 21 days but also received ACTH 120 mg. at the beginning and end of her course of therapy.

The fact that the improvement achieved with hormone therapy is temporary has been noted in this series in agreement with reports of other authors. It has also been noted by previous authors that responses to second courses of therapy are relatively rare and are usually less complete than those following the initial course. However, one patient (B.C.) responded to three courses of ACTH and is now undergoing a fourth remission in response to cortisone. This patient still appears responsive 36 weeks after hormone therapy was first initiated. Another patient (B.A.), who was thought to have become refractory to cortisone, exhibited a second response when higher dosage of this drug was employed six weeks later.

The metabolic effects of ACTH and cortisone have been described in detail in previous studies[8, 10, 23] and will be mentioned only briefly here. Serious toxic or side effects were infrequently encountered. All the patients developed a typical "moon-facies" and all demonstrated salt and water retention. In those instances where the latter was excessive and caused discomfort to the patient, rapid diuresis with alleviation of symptoms could be induced by cessation of therapy for 24 to 48 hours. Therapy was then resumed at previous dosage levels and re-interrupted as indicated. One patient who was treated with cortisone for one month with dosage progressively increased to 300 mg./day developed hypertension and cardiac decompensation. These complications were not noted in any of the other cases. Two patients treated early in the series developed clinical, chemical and electrocardiographic evidence of hypokalemia. Later cases were given 2 to 3 gm. daily of potassium chloride by mouth and no further difficulty was encountered. Two patients developed transient hyperglycemia, but glycosuria was not found. With completion of therapy, patients were usually given added sugar by mouth for several days in order to prevent hypoglycemic reactions. Acne was not encountered but one patient developed moderate hirsutism.

The mode of action of ACTH and cortisone in producing remissions in leukemia is as yet uncertain. Biochemical observations by Pearson et al.[8-10] and Snelling and co-workers[23] have indicated that the effect of the hormones on the blasts is to cause their destruction rather than their maturation to more mature cellular forms. It seems to the authors, however, that the reappearance and regeneration of the normal cellular components of the marrow does not take place merely by virtue of the removal of an encroaching mass of leukemic cells, but possibly as a result of a specific stimulating effect of the hormones. Increased erythropoietic activity of the marrow and striking increase in the numbers of thrombocytes in the peripheral blood have often been evident before any significant reduction in the percentage of blasts in the marrow was discernible. Increased numbers

of neutrophils in the peripheral blood have also been evident before the marrow changed significantly. The simultaneous destructive and stimulating effects of ACTH and cortisone suggest their use in combination with those agents which are basically destructive and depressive to hematopoietic tissue, i.e., folic acid antagonists and ethyl carbamate (urethane). It is possible that all portions of the marrow do not respond synchronously, and the large sampling error in marrow aspirations make interpretation of these observations hazardous. Clinical evidence, however, also indicates that the mechanism by which ACTH and cortisone induce remission is different from that of other antileukemic agents (such as the folic acid antagonists and urethane) for the response of individual patients to the hormones and to other antileukemic agents is not necessarily parallel.

Comment

In considering the place of ACTH and cortisone in the treatment of leukemia, it is felt that there is sufficient evidence to indicate that they constitute a valuable addition to the therapeutic armamentarium. Responses, when obtained, are rapid and dramatic, and are not accompanied by a period of hematologic depression and increased illness as is frequently seen with the use of folic acid antagonists and other leukotoxic agents. In addition, while evidence of hematologic relapse appeared early in several cases, clinical remissions of 4 to 9 months' duration have been observed. While it is not firmly established that hormone therapy prolongs life, the periods of clinical remission are characterized by subjective and objective well being not typical of untreated leukemia in childhood. Finally, evidence in two cases suggests that when resistance to hormone therapy occurs certain patients may still respond to other antileukemic agents.

Summary and Conclusions

The results of treatment of 14 children with leukemia with ACTH and cortisone have been presented. Complete laboratory and clinical remissions lasting 1 to 33 weeks were induced in six patients; incomplete remissions were induced in two others.

No favorable responses were encountered in terminal states, monocytoid leukemia, and granulocytic leukemia differentiated beyond the blast stage. No relationship could be demonstrated between refractoriness to the hormones and to antifolic acid therapy; patients completely refractory to one agent have shown complete response to the other.

Although repeated remissions may be induced by hormone therapy, increasing resistance to the drugs tends to develop. While permanent benefit has not been obtained, ACTH and cortisone constitute valuable additions to the therapy of leukemia.

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Addendum

The significant developments which have occurred since the submission of this paper are listed below. Follow-up extends to May 7, 1951.

Case 2, B.C.—The cortisone induced remission referred to in the case report lasted for only 5 wk. and then complete relapse occurred. A 5 wk. course of combined therapy which included a-methopterin 210 mg., ACTH 400 mg. and cortisone 2000 mg. produced only transient improvement in the marrow. An additional course of ACTH 1500 mg. over a period of 3 wk. was equally unsuccessful. A 16 day course of aminopterin, given at this point with total dosage of 1.8 mg., did however produce a hematologic remission. The toxic symptoms which necessitated the discontinuation of aminopterin were rapidly relieved by the administration of citrovorum factor. After 6 wk., complete relapse was again evident. He was retreated with the hormones, receiving a total of ACTH 1350 mg. and oral cortisone 2500 mg. over a 23 day period. ACTH was given for 4 days at the beginning and end of this course. This technic of therapy was selected because of the favorable response observed in Case 5. The patient is once again in complete clinical and hematologic remission 15 mo. from the time of his initial treatment. This recent favorable response indicates that patients who have become refractory to hormone therapy may after successful treatment with folic acid antagonists regain sensitivity to ACTH and cortisone.

Case 4, J.D.—This patient gradually became refractory to a-methopterin therapy and died 1 yr. following his initial course of hormone therapy.

Case 5, A.M.—After 11 mo. of complete hematologic and clinical remission, relapse occurred. Complete remission again followed a 4 wk. course of therapy consisting of ACTH 360 mg. and cortisone 3400 mg. ACTH was given at the beginning and end of treatment as in the first course. At the present writing, remission persists 14 mo. after the initial course of therapy.

Case 10, D.F.—The a-methopterin induced remission persisted for only 4 wk. Further therapy with cortisone, multiple transfusions, arsenic and additional folic acid antagonists was totally unsuccessful. The patient died 6 mo. after the initial remission had been induced.

Case 14, D.K.—The cortisone remission persisted for 17 wk. With the occurrence of relapse at this time the patient was retreated with ACTH 440 mg. and oral cortisone 2760 mg. over a 30 day period. Improvement was minimal and therapy with folic acid antagonists is now being started.

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SPANISH ABSTRACT

Los Efectos de ACTH y Cortisone en Niños con Leucemias

Los autores reportan los resultados del tratemiento con ACTH y Cortisone en 14 niños con leucemias. Remisiones clinicas y hematologicas de la 33 semanas de duración fueron inducidas en seís pacientes; remisiones incompletas fueron inducidas en otros dos casos.

No se observaron repuestas favorables en los estados terminales de la leucemia, en leucemia monocitica, ni en leucemia granulocitica de tipo undiferenciado. No se demonstró relación alguna entre la repuesta terapeutica de estas hormonas y la del acido folico, pacientes totalmente refractarios a un agente respondieron al tratamiento con el otro.

Los Autores indican que aunque remisiones repetidas pueden ser inducidas con estas hormanas, cierta resistencia al tratamiento tiende a desarrollarse. Finalmente, se estima que pesar de los resultados trasitorios, ACTH y Cortisone constituyen adiciones valuables al tratamiento de las leucemias.

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EFFECTS OF LIMITED HEARING ON THE DEVELOPMENT OF SPEECH IN CHILDREN UNDER THREE YEARS OF AGE

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THE development of speech implies the learning by imitation of the basic phonemes and usually occurs between the ages of 1 and 3. The imitation is evoked by the combined seeing and hearing of normal speech. Through constant visual and auditory stimulation, listening habits are established for all types of sound. These listening habits do not develop normally in children with limited hearing. Under "children with limited hearing" we nowadays classify those who have hearing losses for the range of important frequencies of speech as low as 30 db or up to as high as 80 to 90 db. That is, children with limited hearing are those who have usable hearing in contrast to those who have no usable hearing. The latter are classified as "the deaf."

SCREENING

Inasmuch as the first years of life are the crucial ones for the natural development of speech and language, detection of loss of hearing in a baby is most important. At present there is, in the majority of cases, an infertile delay between the recognition of a hearing impairment and the commencement of therapy or management. Delay means loss of invaluable time during the very period when the child can most easily be helped and further damage prevented. No time should be lost in the building up and the keeping of a memory of sound patterns as well as learning the concept of communication for adjustment to the hearing world. This time lag must be prevented by educating parents, general practitioners and nursery school teachers. New methods of testing should be instituted so that the deafened children are detected and evaluated at the earliest possible age. If this is not accomplished, too many hard of hearing children will eventually be sent to schools for the deaf without having had the chance to overcome their handicap in a normal environment.

Categorization of hard of hearing children involves a dual classification: (1) cases in which the hearing loss is so severe that normal conversation cannot be perceived by the child (60-90 decibels) and (2) the mild cases in which normal conversation can be perceived although often with great difficulty and distortion (30-60 decibels). Those in the latter group are harder to detect with simple speech tests because the vowel sounds and perhaps some voiced consonants may be heard at low intensity levels. In spite of the distortion the child may indicate that he understands many words.

In the severely deafened group, a loss of hearing is discovered more easily because of the frequent lack of response to gross sounds. These children also show very little if any response to conversational voice and a gradual cessation of spontaneous vocalization. In the second group, however, we may expect that some speech will be developed, although

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it will be delayed and defective. In addition, the voice quality may be harsh and monotonous.

The ideal solution for screening out cases of congenital hearing impairment would be a test for every newborn baby. It is known that the newborn will respond by an acousto-palpebral reflex to Urbantschitsch whistles.[1] In our own preliminary experiments one month old babies responded to pure tones as well as to a "white noise." Such a noise contains all the frequencies of audible sound (from 20 up to 10,000 cycles/sec.) in the same intensity.

Other quantitative tests with all kinds of sounds can be done if a calibrated noise level meter is available.

In many cases of hearing impairment acquired during the first three years of life, the parents will notice a marked change in the child's pattern of responses to ordinary home environmental noises. This often involves a change in behaviour patterns and perhaps a loss of certain speech elements already learned. However, cases of slow congenital impairment, which may still be mild at birth, are not likely to be detected until the parents become anxious about a lack of speech or about defects in speech.

We must draw the attention of parents and nursery school teachers to the importance of watching for the baby's earliest responses to a variety of sounds, such as the telephone or other bells, noisemakers, the radio and human voices. In making such observations care should be taken to eliminate the possibility of the baby's reaction being due to the feeling of vibrations or movement of the air, as in the breath stream of speech. If deafness is suspected, a visit to an otolaryngologist who is especially interested in the hearing problems of children or to a speech and hearing clinic should not be deferred. We make a plea to general practitioners to include hearing tests suitable for babies in their routine examinations. The child should be referred immediately for further examination if there is the slightest doubt that hearing is not completely normal. The use of one of the new screening audiometers by all pediatricians would be ideal.

Remedial Training and Education

Twenty-one deafened children under 3 years of age were referred to the Audiology and Speech Section of the Vanderbilt Clinic in the year 1949, this being 20% of the total number of children under 12 referred. A program of remedial training was given individually to each child for an average of one month, once weekly. If the child could benefit from a group situation, he was then placed for two months in a group consisting of 2 or 3 other children of similar age and with similar hearing problems. The program had four primary goals which were achieved as listed below.

1. To test as accurately as possible the child's hearing level for pure tone throughout the speech range. This is done by using conditioning technics if the child is too young to indicate that he hears by the usual verbal or gesture responses. A very young child can as a rule be trained to move a toy or look up at a puppet when he hears a sound[2] or, if this fails, a more objective technic, the psychogalvanic skin resistance test,[3] can be employed.

2. To establish a basic understanding of lip movements and facial expression (generally known as "lip reading" or better—"speech reading"). To achieve this objective in a natural way, games and daily activities were used.

3. To stimulate the child's awareness of sounds. This was done by using various

FIG. 1. Play therapy as introduction to sounds through wearing of hearing aids in small children. Aid is worn in pouch about child's neck. Teacher also wears pouch to encourage children. Parents watch methods and, ideally, are not in same room. (Photograph by Lawrence G. Heinrich, New York City.)

noisemakers, by receivers attached to a radio or phonograph, by amplified speech, and by rhythmic activities to a background of amplified music.

4. To train the child to wear an individual hearing aid. This program would have failed if the parents and their children had not been trained together. Parents gained a knowledge of the problems of limited hearing and they learned to use every opportunity to help their children lead normal lives. This parent hygiene was accomplished in several ways (Fig. 1):

1. By observing the training period
2. By working and playing with the child together with the therapist
3. By group discussion and personal conference
4. By typewritten suggestions for home training

Of great value to the parents and therapists was a diary kept by the parent of the child's daily reactions to and problems connected with home training.

For example, the mother of Anita reported in September 1949 that Anita (aged 2 years, 6 months), who has a loss between 60 and 70 decibels for the most important frequencies in speech (chart 1), was restless and excitable and showed no real response to or interest in sounds. In November, after 10 weeks of the program just outlined, the report was: "I have been noticing a change in Anita. She is so much more aware of sounds, and keeps drawing my attention to them. She seems quieter and less tense. This morning she climbed into our bed and woke us up by saying 'Boo' very plainly. She was elated with

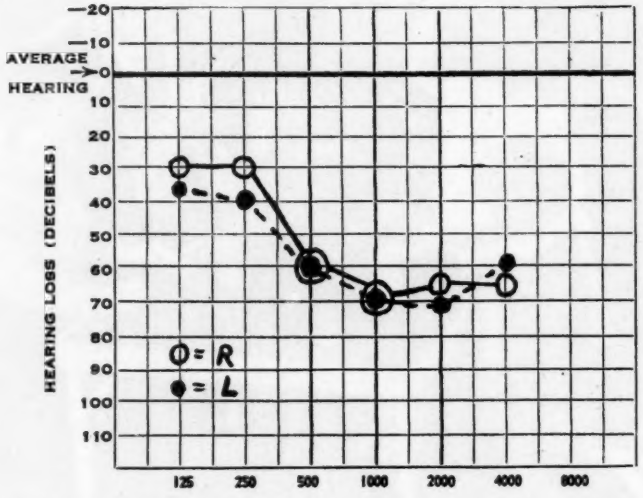

CHART 1. Audiogram of Anita, aged 2 yr., 6 mo., with some low tone deafness and moderately severe high tone deafness, who benefited remarkably from speech work and hearing aid.

the sensation she caused." In February 1950, the report was: "Anita seems to be delighted to have her hearing aid. She laughs, pats her chest, and points to her ear, talking as fast as she can. She and her daddy have great fun babbling into it. When he changes words, she attempts to copy the sound and 'baby' is quite different from 'bye-bye.' She loves to hear music and picks up her skirt and goes dancing around."

Carol, aged 2 years, with an average loss of 90 decibels, had been playing toy animals as her mother imitated their sounds. Suddenly, Carol picked up the cow, put her hand on her throat and said "mm-moo." Her previous sounds had been grunts made on inspiration.

The change in older preschool children is equally gratifying. Four months after training commenced, the mother of Ira, whose average loss is 75 decibels (chart 2), reported: "His talking is much improved and he seems to understand questions much better. He seems to be growing up more and to be losing his baby ways. Today he heard the sound of the wind blowing through the trees. He immediately wanted to know what that was."

Whereas Paul previously listened dully to victrola records, his mother reported: "He now shows a great many more facial expressions."

After the three month program outlined above, the child has as a rule been trained to wear a hearing aid, so the specific aid with which the best responses were obtained in

the clinic is selected. The parents then purchase this hearing aid and are given a definite home training program for its use combined with speech reading. After a few more months the child will be wearing his own instrument for some hours daily because he is gradually learning to recognize its value. Further formal training is postponed until it is found how much the child learns spontaneously at home, now that he can more or less hear normal speech with his aid. During this period, attendance at a nursery school for normal hearing children is fundamental and essential since natural speech development cannot take place when young hard of hearing children are exclusively educated together and continuously hear one another's abnormal speech. Moreover, they always build up an

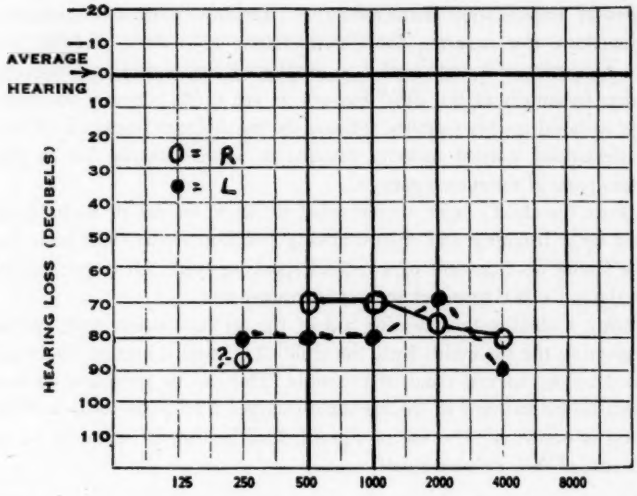

CHART 2. Audiogram of Ira, aged 5 yr., with severe nerve deafness for all frequencies, sufficiently rehabilitated to go to regular school.

expressive gesture language upon which they become dependent. Hard of hearing children in a normal school are continually stimulated by natural speaking voices so that they acquire a memory for normal speech elements and are motivated to communicate with these elements rather than with gestures which are often meaningless except to an intimate.

HEARING AIDS

The problems connected with hearing aids for very young children occur in the selection of the most suitable hearing aid, rather than in training the child to wear one. As long as the problem for prescribing hearing aids for adults has not been satisfactorily solved, it is not possible to give a definite procedure for the very young child. Some factors may be mentioned: the aid should be small; batteries, microphone and amplifier should be in a single unit and it should give sufficient amplification with low distortion. Until recently the amount of amplification was closely connected with the size of the individual hearing aid, but fortunately the latest developments have made available very small aids which give high gain and this has changed completely the approach to the very young child's problem.

As regards the sound quality produced by the aid, it is of paramount importance that

the reception of sounds be as natural as possible, since in most cases the child, by using the hearing aid, will hear speech sounds for the first time in his life. This means that every effort should be made to amplify all frequencies so that regardless of the child's type of loss the final result is a high fidelity reproduction. If the child has the common greater loss in the high frequencies (chart 1), these should be amplified more than the low frequencies, while if the loss is equal for all frequencies the amplification should be the same for all frequencies, that is, "flat." (See chart 2.)

However, at the very beginning the child will only hear what are to him a jumble of unrelated noises. He will not perceive fine differences between speech sounds. This discriminating function has to be built up gradually. It has been found useful to use various types of amplification characteristics in teaching children to recognize the more difficult phonemes. For instance, for discrimination of sibilants and the voiceless and explosive consonants, it is very useful to emphasize the high frequencies by adjusting the amplifier. Inasmuch as the child has not as yet a real memory for speech sounds, we are able to build up his memory without the psychologic resistance offered by adults who have developed warped memory patterns of speech sounds due to their inability to hear certain parts of the speech pattern.

Finally, since the child's voice mirrors what he hears, the use of an individual hearing aid to build up a listening and discriminating function is the most basic factor in the success of a future development of a natural speaking voice. Of course, all this training depends on the individual type and amount of hearing loss.

When fitting a child with a hearing aid of the air conduction type, special attention should be given to the ear mold. Since the child's ear canal is narrow, the high tones may be attenuated by the narrow canal of the mold. This can be prevented by using a short tip. Inasmuch as the anatomy of the ear canal changes, a frequent recheck of the tightness of the fitting is necessary. The use of tips of flexible material seems to be indicated in children because of their delicate meati.

Summary

Natural development of speech elements in acoustically handicapped children has been proved possible provided that the limited hearing is detected at a very early age by new testing procedures. It is achieved under clinical conditions by the use of individual hearing aids which provide auditory stimulation from the age of 2 years, or even earlier, upwards. Special treatment is necessary and training of the parents plays an important part. If a listening function is not established at an early age, there is the danger that children with limited hearing will ignore sound or will actually find it annoying. Future success is dependent on the hard of hearing child's being educated together with the normal speaking children, with the reservation that he will need special arrangements for speech therapy and speech reading. New specifications should be made concerning the admission of acoustically handicapped children into special schools and the considerations mentioned above should be applied.

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SPANISH ABSTRACT

Los Efectos de Deficiencias Auditivas Limitadas Sobre el Desarrollo del Habla de Niños Menores de Tres Años de Edad

Los autores estiman que el desarrollo natural de los elementos del habla de niños acústicamente deficientes puede ser posible siempre que esta sordera sea descubierta a una edad temprana y rectificada con aparatos para oir, los cuales provocan la estimulación auditiva desde la edad de dos años en adelante. Un tratamiento especial es necesario y la educación de los padres juega un importante papel. Si la función auditiva no es establecida a una edad temprana se corre el peligro de que los niños con deficiencia auditiva ignoren sonidos o los encuentren mortificantes. El éxito futuro depende de la enseñanza colectiva de estos niños con sordera y niños normales, con un cuidado especial en la enseñanza del lenguage hablado y lectura de labios. Finalmente se indica la necesidad de una revisión en la enseñanza de los niños con defectos auditivos en escuelas especializadas y la aplicación de los conceptos arriba mencionados.

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AUREOMYCIN IN THE TREATMENT OF FIBROCYSTIC DISEASE OF THE PANCREAS

Clinical and Metabolic Studies

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THE efficacy of aureomycin as an adjunct in therapy of fibrocystic disease of the pancreas has previously been reported.[1] The generally poor prognosis[2-5] for this disease, however, makes it desirable to reassess any therapeutic agent at reasonable intervals. Understandable confusion has resulted from trials and claims as new antibiotic agents have become available for clinical use.

There seems little doubt that symptoms have been ameliorated and prognosis improved to some extent by the use of the newer antibiotics.[3-5] However, most of the patients with this disease have required repeated or continuous therapy and losses of effectiveness of these agents because of the development of bacterial resistance have been repeatedly observed.[6,7]

This report is concerned with an evaluation of aureomycin as the sole agent in treatment of fibrocystic disease of the pancreas over periods of from 12 to 24 months. The decision to use this drug alone—without even such usual adjuvants as pancreatin—was based on studies of nitrogen metabolism under the influence of aureomycin early in the course of this work.

PLAN OF STUDY

Seventeen children were studied, ranging in age from 2 mo. to 7 yr. Though the severity of clinical manifestations varied widely, the diagnosis in each case was based on the demonstration of the consistent absence of trypsin from duodenal contents.[8,9] Respiratory features varied from none to far advanced bronchiectasis. All patients were hospitalized at the start for necessary clinical, laboratory and roentgenologic studies; at the same time an evaluation of general behavior, appetite, temperature and bowel function was made. After initial trials, an empiric dosage schedule of aureomycin 25 mg./kg. body weight/day was arrived at. The total daily dose was administered in 2 to 4 equal portions, with meals, either in capsule form or as spersoids®, the latter being introduced into the formula for the infants. The authors gained the impression, and still believe, that amounts in excess of this were unnecessary, neither accelerating nor increasing the degree of improvement observed. The only dietary restriction was the elimination of gross fats. All diets were supplemented with high potency water soluble multivitamin preparations* calculated to furnish about 3 times recommended daily intakes of fat-soluble vitamins. After completion of baseline studies and preliminary dietary adjustments, these children were followed at frequent intervals in the outpatient departments.

Of necessity, considerable weight had to be given to reports of parents as to behavior, appetite and intercurrent disease. All parents were most cooperative and kept carefully written records.

Of the 17 patients, 10 were male and all were white. Five were first born, with no familial history of similar disease. The disease had been previously recognized in the siblings of 7 patients, and there was no evidence of familial occurrence for the remaining 5. At the start of the study all patients were manifestly small and poorly nourished; all but one fell into the "three percentile" group according to the scales of the Boston Infant's Hospital. Only 3 patients lacked objective evidences of progressive

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* A large variety of proprietary preparations was used.

respiratory disease; 2 of these were infants. In 6 children clinical and roentgenologic evidence of bronchiectasis was present. Of the remaining 8 subjects all had peribronchial fibrosis as judged by serial roentgenograms, but the clinical manifestations of pulmonary disease varied greatly. There was a general correlation between severity of respiratory disease and age.[10]

Results

Mortality: Two children died. The first one died of pertussis at the age of 19 months after aureomycin had been given continuously for 6 months, during which period there had been considerable symptomatic improvement despite roentgenographic evidence of progressive bronchiectasis. Autopsy confirmed the diagnosis of fibrocystic disease of the pancreas with advanced bronchiectasis, and revealed massive infection of the respiratory tract by H. pertussis. The second child had far advanced bronchiectasis when therapy was started. Considerable clinical improvement was noted during 12 months of therapy, and no progression of the lung lesions could be seen in RGs. Her parents believed she had improved sufficiently to allow her to attend school. She died rather suddenly at the age of 6 years with terminal evidences of myocardial failure justifying a clinical diagnosis of cor pulmonale secondary to bronchiectasis. No autopsy was secured.

Respiratory Symptomatology: Three children who lacked evidences of respiratory disease when therapy was started still appear to be entirely normal after periods of 13 and 14 months. By and large, the 8 children who had minimal respiratory symptoms at the onset of aureomycin therapy have had no more than transient colds and sore throats. One child had a single bout of acute streptococcal tonsillitis for which penicillin was temporarily added to the therapeutic regime. Another had typical, moderately severe rubeola. The pulmonary symptoms of rubeola in this child were no more severe than usual; aureomycin therapy was not interrupted. None of the other six children in this group have had fever at any time during periods of aureomycin therapy ranging from 12 to 19 months. Clinically all appear improved though serial RGs appear to have shown no significant changes.

Of the remaining four living patients, all of whom had advanced pulmonary disease when therapy was initiated, each has offered subjective and objective evidences of improvement. On the average "days of fever" decreased from 20 per month before therapy to 4 per month afterwards. Patient days of hospitalization were reduced to zero. Two of these children had typical uncomplicated rubeola, during which there was no interruption of treatment. Serial RGs have not shown any significant changes and there has been no real indication to repeat lipiodol bronchograms. Two of these children, previously restricted to home, and there largely to bed, now attend school regularly.

Nutritional Effects: Weight gain and growth were gratifying in all cases. Table 1 sets forth data as to weight gain for periods immediately before and after treatment; in general rapid increments during the first few months were followed by slowing to more usual rates thereafter.

Appetite: Neither the parents nor the authors noted any marked deviation from the characteristic polyphagia except for expected transient failures during infrequent febrile episodes.

Feces: Except for diminution in fat content with initial adjustment of diets, there were no alterations in the character of the stools; these were typically bulky, foul and frequent.

Pancreatic Function: As measured by repeated assays for trypsin in the duodenal contents, no change was noted.

TABLE 1

CHANGES IN BODY WEIGHT, BEFORE AND AFTER TREATMENT WITH AUREOMYCIN (R)

Pt.	Age	Gain in Previous 6 mo., kg.	Wt. at Start, kg.	Mo. of Therapy	Total Gain kg.	Mean Gain/mo. kg.
M.D.	2 mo.	—	2.7	14	8.6	0.6
M.B.	3 mo.	—	4.3	12	10.4	0.9
L.K.	3 mo.	—	3.2	14	9.5	0.7
C.H.	6 mo.	0.5	3.6	17	9.5	0.6
M.D.	9 mo.	0.9	3.6	13	7.3	0.6
P.N.	13 mo.	0.9	5.2	6	4.1	0.7
R.N.	15 mo.	1.3	6.4	12	4.5	0.4
J.L.	19 mo.	0.9	7.7	14	6.4	0.5
M.G.	24 mo.	1.3	7.3	16	7.3	0.5
J.S.	27 mo.	0.5	12.2	14	2.3	0.16
D.R.	30 mo.	0	11.8	18	4.1	0.22
M.F.	32 mo.	0	10.9	14	5.0	0.35
R.C.	3 yr.	0	10.9	24	7.3	0.30
J.R.	3½ yr.	0	12.2	19	6.8	0.35
R.C.	5 yr.	0	13.2	19	5.0	0.26
R.P.	6 yr.	0	16.3	12	3.6	0.30
J.B.	7 yr.	0	14.5	23	7.3	0.31

Personality and Behavior: Though reports were admittedly difficult to divorce from wishful thinking, all parents told of "remarkable" improvements. The authors were gratified by very apparent changes as well and felt they were largely due to relative freedom from infection, to greater physical and social activity, and to the happier outlooks of all involved resulting from rather obvious somatic improvements.

Reactions to Aureomycin: No undesirable side effects were encountered in this group of patients. One child sneezed while chewing a capsule of aureomycin and had severe rhinorrhea for an hour afterward.

Reduction in dosage of aureomycin to levels below 25 mg./kg. daily, or complete withdrawal of the medication, was followed in each instance, within a period of 3 to 4 days, by an exacerbation of previous respiratory symptoms; return to the full dosage regime then as quickly accomplished the same favorable responses as were initially encountered. No difference was noted when the total daily amount was administered in 2, 3 or 4 portions.

Nitrogen Balance: When growth responses were noted, an attempt was made to obtain objective measurements of this interesting effect; similar gains in weight had not been previously observed when the respiratory component of this disease had been controlled with other agents. The decision to study nitrogen metabolism resulted from the thought that the observed weight gains might be mirrored by improved efficiency in utilization of protein.

Eight nitrogen balance studies were performed, using four patients (P.N., R.P., R.C., J.B.). Each child was studied for two periods. In the first no therapy was given and during the second period they received aureomycin (25 mg./kg. body weight/day divided into 4 equal doses). Prior to and during the first period respiratory symptoms were minimal. Collection periods ran for nine consecutive days, the feces being marked with carmine

TABLE 2

AVERAGE VALUES FOR NITROGEN

Patient	Age in Yr.	Wt. in kg.	Total Ingested N gm./kg./24 hr.		Absorbed N* gm./kg./24 hr.		Urinary N gm./kg./24 hr.		Fecal N gm./kg./24 hr.		Nitrogen Balance gm./kg./24 hr.	
			Control	Aureomycin	Control	Aureomycin	Control	Aureomycin	Control	Aureomycin	Control	Aureomycin
R.P.	5	15.9	0.67	0.98	0.37	0.69	0.28	0.31	0.32	0.29	0.075	0.39
P.N.	1	5.7	0.81	1.21	0.38	0.96	0.42	0.28	0.44	0.25	−0.064	0.69
R.C.	3	11.4	0.48	1.16	0.23	0.78	0.18	0.30	0.25	0.39	0.058	0.47
J.B.	7	16.8	0.53	0.92	0.24	0.78	0.15	0.19	0.32	0.25	0.056	0.52
Mean and Sigma ±			0.62±.14	1.07±.10	0.30±.09	0.80±.12	0.26±.09	0.27±.05	0.33±.05	0.30±.05	0.031±.056	0.52±0.10
Probability of difference by chance			P<.001		P<.001		P<.8		P<.7		P<.001	

* Absorbed N = Total Ingested N − Fecal N.

at the beginning and end of each. Total outputs of urine and feces, and aliquot portions of the diet were analyzed daily for nitrogen content by macro-Kjeldahl technic. The children were offered a diet low in fat and high (30% by weight) in protein and were allowed to eat *ad libitum*.

The patients were hospitalized for the collection periods.

Results are presented in table 2. Values shown are averages over an experimental period for each child, expressed as grams of nitrogen/kg. body weight/24 hours. The discussion to follow refers to mean values for all four children considered together.

With aureomycin there was about a 14-fold increase in the amount of N retained—from 0.036 gm. to 0.5 gm. This is attributed to three factors:

1. An increase in the amount of N voluntarily ingested, from 0.62 gm. to 1.07 gm. During control periods protein eaten comprised 3.6% of the weight and 12.6% of calories in the total diet. With aureomycin the corresponding values were 4.4 and 15.9%.

2. An increase in the amount of N absorbed, from 0.3 gm. to 0.8 gm. This is indicated by the slightly decreased amount of N in the feces despite the increase in N ingested.

3. An increase in utilization of absorbed nitrogen.[11] This is best expressed percentage-wise:

$$\frac{\text{Retained N*}}{\text{Absorbed N}} \times 100 = \text{per cent absorbed N utilized}$$

This value increased from 12% in control periods to 65% during therapy. This is also seen by contrasting the slight increase in urinary N (0.01 gm.) with the large (0.5 gm.) increase in absorbed N. In one child (P.N.) there was an actual decrease in urinary N and an increase in absorbed N.

Discussion

The clinical improvements are essentially in agreement with those described by Shwachman et al.[1] A search of the literature fails to reveal similar results when any other agent or combination of agents has been used.[2-5]

Gratifying as are these clinical responses, it is the mode of action of aureomycin that lends itself to interesting speculation. Its antibiotic powers have been extensively elucidated, and that some of the clinical effects noted result from control of infection is apparently without doubt. Several factors, however, mitigate against acceptance of this single factor as an explanation for all observed effects. It has been shown that bacteria in the respiratory tract of patients with this disease develop considerable resistance to aureomycin within much shorter periods than that covered by this study.[7] Still, after periods extending up to 24 months these patients continue to respond well to aureomycin. Observations in this laboratory indicate that there is no remarkable early change in the respiratory bacterial flora after aureomycin is given.

Similar growth responses and effects on nitrogen balance have not been described following the use of other antibiotics. It is not possible to explain these beneficial and apparently "nonantibiotic" effects of aureomycin at this time. It is tempting to speculate on their relationship to the observed "growth factor" of aureomycin as described in animals.[12] However, both the nature and mechanism of action of the "growth factor" are still unknown.

* Retained N = Intake − (Fecal + Urinary Output)
Absorbed N = Intake − Fecal Output

The results of these studies of nitrogen balance offer two points of interest not previously noted by others.[13,14] Despite their large appetites and despite the fact that their diet was rich in protein, these children voluntarily ate inordinately small quantities of this foodstuff. The amounts corresponded closely to those one would expect were only protein-poor food eaten. Clinically, these children's greatest dietary need seems to be for protein. The data suggest that these patients selectively avoid protein for reasons not yet known.

Even during control periods, values for utilized protein were considerably greater than those previously published for normal children.[11] This apparently greater ability to utilize even limited protein intakes suggests some type of compensatory or conserving mechanism.

Further studies of the mechanisms by which aureomycin aids in protein utilization by these patients may furnish valuable additional information on the nature of this disease.

Summary

A group of patients with fibrocystic disease of the pancreas was treated with aureomycin over periods of 12 to 24 months. Gratifying clinical improvement and increases in utilization of dietary protein were observed.

Acknowledgment

The authors are indebted to Miss M. L. Pesut, Charity Hospital dietitian, for her invaluable assistance.

Case Reports

A few brief protocols will serve to illustrate a number of problems common to the entire group.

Case 1. J. R. was first seen at the age of 3½ yr. because of "chronic pneumonia." Poor weight gain and frequent foul stools had been observed before he was 3 mo. old, and since his fourth or fifth month he had rarely been free of respiratory symptoms. Treatment in the past had consisted in the main of penicillin and sulfonamides given in varying combinations and by various routes. He was small, hypotonic and poorly nourished; dyspnea, cyanosis and physical signs of extensive bronchopneumonia were present. Chest RGs showed rather typical increased interstitial densities, peribronchial thickening, emphysema and coarse hilar markings. Duodenal contents contained no trypsin, and steatorrhea was marked. Staph. aureus hemolyticus was the predominating organism in cultures of sputum.

After 10 days of unsuccessful therapy with penicillin, sulfonamides, oxygen and symptomatic measures, aureomycin was given; fever, cough and dyspnea subsided within 3 days and he was discharged from the hospital shortly thereafter. In 20 mo. of continuous aureomycin therapy since that time, he has gained 6.8 kg. in weight and has had only minimal and infrequent respiratory symptoms. An intercurrent attack of rubeola was mild and uncomplicated. Serial RGs have shown no remarkable changes except for questionable decrease in density of interstitial hilar markings.

Case 2. R. C. was first diagnosed as having fibrocystic disease of the pancreas at 11 mo. of age, after a 6 mo.-long classical nutritional and respiratory history. For the next 2 yr. treatment consisted of frequent administration of sulfonamides and penicillin and the use of pancreatin, despite which he grew slowly, had almost continual respiratory symptoms, and had, on the average, 15 "days of fever"/month. Serial RGs showed a progressive increase in the density of the perihilar shadows. At 3 yr. of age, when aureomycin therapy was started, he weighed 10.9 kg., although his development had been otherwise normal. During the first month of therapy he gained 1.8 kg. in weight, there was a complete subsidence of respiratory symptoms, and he had no "days of fever." He has remained asymptomatic and afebrile in the 24 mo. which have followed. Serial RGs have shown no progress of the pulmonary lesion. On his last visit, at the age of 5 yr., he weighed 16.3 kg.

Case 3. R. P., a 5 yr. old girl, was brought to Charity Hospital because of pneumonia severe enough to cause coma. Dyspnea, cyanosis and extensive respiratory signs of pneumonia were present

to a marked degree, and severe pulmonary osteoarthropathy gave evidence of the chronicity of the condition. Historically it was determined that she had gained weight slowly since birth, that respiratory symptoms had first appeared at about 18 mo. and had been continuous since; at this time foul, bulky, odorous stools were first noted. Clubbing of the fingers was first noted at 3 yr. Treatment with penicillin, sulfadiazine and oxygen was started on admission, but these and a procaine splanchnic block failed to aid her materially and aureomycin was administered. In 48 hr. she was afebrile and felt well enough to leave bed. Trypsin was absent from the duodenal contents; steatorrhea was marked. Chest RGs revealed a diffuse bronchopneumonia and marked increases in the bronchovascular markings; bronchograms revealed cylindric bronchiectasis of a severe degree in the right middle and lower and the left lower lobes. Aureomycin was discontinued and splanchnicectomy was performed, but 10 days postoperatively there was a violent recrudescence of her respiratory symptoms and aureomycin was again given, and again a rapid subsidence of fever and symptoms was noted. She continued to take aureomycin for the next year, during which time she remained relatively well. She gained 2.7 kg. in weight and began to attend school. Serial RGs showed no significant changes. After 1 yr. of therapy she suddenly developed signs and symptoms of acute heart failure and died shortly thereafter. No autopsy was obtained. The clinical diagnosis was cor pulmonale secondary to severe bronchiectasis and fibrocystic disease of the pancreas.

Case 4. M. B., a 3 mo., 4.3 kg. girl, was referred for splanchnicectomy, the diagnosis of fibrocystic disease of the pancreas having been made elsewhere. Respiratory symptoms were first noted at the age of 3 mo., and no response had been effected by the use of sulfonamides and penicillin. Physical examination revealed emaciation and numerous rales throughout all areas of the lungs; chest RGs showed a diffuse bronchopneumonia. Trypsin was absent from the duodenal contents and the stools. Splanchnicectomy produced no alteration in her condition and a severe attack of pneumonia 3 wk. postoperatively made aureomycin therapy mandatory. She rapidly recovered from the pneumonia, and with continuous therapy has remained well in the 12 mo. since. Serial RGs have shown the pneumonia to be permanently resolved and there have been no other changes. Her development has proceeded normally, and at 17 mo. of age she weighs 10.9 kg.

Case 5. M. D., at 2 mo. of age, weighed 2.8 kg., less than his birthweight despite a voracious appetite, numerous changes in formula and large quantities of vitamins. At 2 mo. mild coryzal symptoms were first noted. Physical examination revealed, in addition to the malnutrition, a few scattered crepitant rales throughout all portions of the lungs. He was afebrile. Chest RGs showed no abnormalities. Trypsin was absent from the duodenal contents on 3 occasions and from the stools on 5. Steatorrhea was marked. Aureomycin was started shortly after the diagnosis was confirmed and there was a gratifying response in weight gain. At 3½ mo. of age he weighed 4.5 kg. and he continued to gain steadily, though somewhat more slowly, thereafter. At 6 mo. of age aureomycin was discontinued for a period of 3 wk., but the appearance of pneumonia necessitated its reinstitution, and it has been given without interruption since then. The entire period of observation has covered 14 mo. At the age of 16 mo. he weighs 11.3 kg.

Case 6. P. N. was admitted to the hospital at the age of 11 mo. for the third exacerbation of "chronic pneumonia." She was markedly wasted, weighing 4.8 kg.; dyspnea and cyanosis were noted and numerous crepitant rales were heard through all portions of the lungs. Chest RGs revealed diffuse bronchopneumonia and marked thickening of the bronchovascular markings. Lipiodol bronchograms showed a minimal cylindric dilatation of the bronchi of both lower lobes. Absence of trypsin from the duodenal contents and the stools, which were otherwise normal in appearance, confirmed the impression of fibrocystic disease of the pancreas. She improved under penicillin therapy and a splanchnicectomy was performed. Recrudescence of her respiratory symptoms 3 wk. postoperatively necessitated the use of aureomycin. She became asymptomatic and afebrile in 5 days. She was discharged from the hospital shortly thereafter, on continuous aureomycin therapy. She remained afebrile and relatively symptomatic for 6 mo., and then contracted pertussis and rapidly succumbed. Autopsy confirmed the diagnosis of fibrocystic disease of the pancreas with bronchiectasis, and cultures from the bronchial secretions yielded almost pure cultures of H. pertussis.

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SPANISH ABSTRACT

Aurecmicina en el Tratamiento de la Fibrosis-Cistica del Pancreas; Estudios Clinicos y Metabolicos

Un grupo de pacientes con enfermedad fibrocitica del pancreas fueron tratados con aureomycin por periodos de doce a veinticuatro meses. Se observaron mejorias clinicas muy halagadoras y un aumento en la utilizacion de las proteinas de la dieta.

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DEVELOPMENT OF NEONATAL ELECTROLYTE HOMEOSTASIS

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CLAUDE BERNARD[1] generalized that the degree of an organism's independence of its environment is proportional to its ability to maintain constant its internal environment. He stated it thus, "Vital mechanisms have one object, preserving constant the internal environment." Cannon's word "homeostasis"[2] well describes this principle, the tendency to maintain a "steady state."

Previous reports from this laboratory[3,4] of a study of the acid-base balance of a group of 73 premature infants revealed a tremendous range of values for these particular infants regardless of age (up to 2 months), maturity or weight (up to 2.3 kg), as compared to adult values obtained in the same laboratory with the same methods.

Various blood chemical studies have been made of cord blood at birth[5,6] and of infants during the first few days of life.[7–10] However, no study has been reported of serial acid-base balance studies of individual full term infants during the first few hours of life.

This paper is concerned primarily with the demonstration of the development of electrolyte homeostasis in the normal newborn infant as compared with standards established for premature infants and for adults.

MATERIAL AND PROCEDURE

Forty-three normal newborn infants were studied. All infants included remained well during the neonatal period and were, so far as could be determined clinically, developing into physiologically normal infants. Mothers' ages ranged from 19 to 38 yr. and previous pregnancies from 0 to 9. Capillary blood samples were drawn (under oil) from the heel for "acid-base" balance, i.e., pH, CO_2, plasma chloride, total serum protein and total base. "R" was obtained by subtraction of the above named acid components from the total base values.

Blood for chemistry was obtained from all infants during the first hour of life. Of every 4 infants, 1 was sampled again at 4 hr., 1 at 8, 1 at 12 and 1 at 24. Thus a complete picture of the electrolyte pattern of each individual was obtained at least twice within the first day of life.

With 2 exceptions all infants studied were born of mothers who received either caudal or saddle block analgesia. (The 2 exceptions: Col, born of cesarian section with local anesthesia, and Ros, delivered by the so-called Reade method.) Birth weights ranged from 2.4 kg. to 4.2 kg.

METHODS

Sampling Technic: The capillary blood sample was collected in an Exton blood plasma tube.*[11] The centrifuge tube had been coated with heparin in the following manner: the tube was filled with

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* Obtainable from Scientific Glass Apparatus Co., Bloomfield, N.J.

TABLE 1

FULL TERM INFANTS ACID-BASE BALANCE

Code	pH		Total CO_2 Content mEq./l.		Plasma Chloride mEq./l.		Total Serum Protein gm. %		Total Serum Protein mEq./l.		Total Base mEq./l.		"R" mEq./l.	
	Birth	4 hr.	Birth	4 hr.	Birth	4 hr.	Birth	4 hr.	Birth	4 hr.	Birth	4 hr.	Birth	4 hr.
Col	7.32	7.38	21.3	20.4	106	105	6.17	5.32	15.0	12.9	151	153	10	34
Har	7.32	7.37	23.6	22.0	108	108	6.52	6.34	15.8	15.4	159	156	13	12
Mue	7.30	7.39	17.3	18.4	105	106	6.52	6.52	15.8	15.8	151	153	14	14
Bar	7.30	7.39	22.6	22.5	106	106	6.17	5.83	15.0	14.2	148	149	6	7
Jad	7.27	7.47	11.2	15.5	100	101	5.83	5.49	14.2	13.3	151	149	26	19
Hog	7.39	7.41	21.9	21.6	102	103	6.52	6.52	15.8	15.8	150	151	11	12
Woo	7.28	7.47	14.0	19.7	103	103	6.17	6.17	15.0	15.0	152	150	21	13
Orr	7.35	7.41	19.8	19.3	106	105	6.00	5.66	14.6	13.7	155	154	16	17
Omo	7.36	7.39	18.8	18.6	109	100	6.52	6.17	15.8	15.0	152	149	9	16
Jun	7.20	7.33	13.2	14.2	101	102	6.34	6.34	15.4	15.4	152	153	23	22
	Birth	8 hr.	Birth	8 hr.	Birth	8 hr.	Birth	8 hr.	Birth	8 hr.	Birth	8 hr.	Birth	8 hr.
Lam	7.35	7.45	18.7	21.8	109	110	6.17	6.00	15.0	14.6	151	153	9	8
Ral	7.35	7.40	22.0	21.8	108	108	5.66	5.83	13.7	14.2	156	152	14	9
Kob	7.27	7.47	23.0	21.0	107	106	5.83	5.49	14.2	13.3	155	156	12	17
Fla	7.35	7.43	21.4	21.0	105	105	6.69	6.52	16.3	15.8	156	154	14	13
Whi	7.33	7.43	19.5	20.9	104	106	6.00	6.00	14.6	14.6	152	149	15	8
Rob	7.37	7.42	23.2	22.4	106	107	6.00	5.83	14.6	14.2	156	158	13	15
Bou	7.34	7.39	23.6	21.5	101	104	6.34	5.49	15.4	13.3	155	156	16	18
Pru	7.30	7.35	19.2	20.2	105	104	5.83	6.00	14.2	14.6	151	152	14	14
Den	7.38	7.44	18.9	18.8	104	103	6.17	6.00	15.0	14.6	150	152	13	16
Hol	7.31	7.38	18.6	16.8	107	105	6.17	5.83	15.0	14.2	151	156	12	21
Ern	7.35	7.35	22.4	22.4	109	109	6.00	5.83	14.6	14.2	156	156	11	12
	Birth	12 hr.	Birth	12 hr.	Birth	12 hr.	Birth	12 hr.	Birth	12 hr.	Birth	12 hr.	Birth	12 hr.
Pat	7.37	7.42	20.0	20.1	105	105	6.00	5.66	14.6	13.7	159	152	19	14
Car	7.28	7.41	22.0	18.1	103	105	6.69	7.03	16.3	17.1	152	153	12	14
Nie	7.35	7.48	17.0	17.2	103	103	6.17	6.17	15.0	15.0	152	152	17	18
Bec	7.35	7.49	20.0	22.1	105	106	6.00	5.32	14.6	12.9	154	154	16	14
Swa	7.34	7.50	16.2	19.4	101	102	6.00	6.00	14.6	14.6	154	154	23	18
Van	7.33	7.45	23.1	21.1	102	104	6.00	6.17	14.6	15.0	154	154	17	15
Goo	7.41	7.45	18.9	18.3	105	105	6.34	6.17	15.4	15.0	152	152	13	14
Wat	7.36	7.47	18.4	19.6	100	106	5.83	5.83	14.2	14.2	155	160	23	21
White	7.39	7.46	19.4	19.3	102	104	5.83	5.49	14.2	13.3	153	155	18	19
Wis	7.29	7.38	21.6	17.8	106	105	5.66	5.49	13.7	13.3	160	—	20	—
	Birth	24 hr.	Birth	24 hr.	Birth	24 hr.	Birth	24 hr.	Birth	24 hr.	Birth	24 hr.	Birth	24 hr.
Spa	7.48	7.36	20.8	20.2	101	104	6.52	6.00	15.8	14.6	151	150	14	12
Fre	7.37	7.49	22.4	24.9	104	105	5.83	6.34	14.2	15.4	152	159	13	17
Tao	7.36	7.48	19.1	18.6	106	105	6.17	6.17	15.0	15.0	155	151	15	13
Joh	7.33	7.41	23.6	22.5	103	103	6.52	6.17	15.8	15.0	156	154	15	14
Sch	7.42	7.50	21.2	23.2	109	111	6.00	5.32	14.6	12.9	155	155	11	9
Sea	7.29	7.36	20.9	19.5	102	108	5.66	5.83	13.7	14.2	151	153	15	12
Jub	7.37	7.37	22.6	22.7	103	107	6.17	5.83	15.0	14.2	151	156	12	13
Law	7.42	7.48	18.3	16.1	107	110	5.83	6.00	14.2	14.6	155	160	16	20
Mil	7.30	7.43	18.3	20.8	102	102	5.66	5.15	13.7	12.5	150	147	17	13
Dav	7.33	7.44	19.2	18.7	104	103	6.17	4.97	15.0	12.1	155	154	18	21
Wel	7.34	7.40	19.1	21.2	102	102	6.17	5.55	15.0	12.5	151	153	16	18
Ros	7.37	7.41	24.5	19.2	—	—	—	—	—	—	—	—	—	—

4 cc. of 40 mg./100 cc. heparin solution and then placed in a vacuum oven* at 65° C. and under the diminished pressure of a water aspirator until dry.

Analytic Methods: Samples were kept at 0°C. until the analyses were performed. That portion to be used for pH determination was sucked into a tuberculin syringe (1 cc.) through a 5.0 cm. hypodermic needle. The air in the syringe was replaced by a small amount of mineral oil covering the sample.

Blood pH was determined using the Cambridge Electron-Ray pH Meter (Research Model).† The meter was kept in an incubator (Liedberg Anhydric Incubator) which was maintained at a temperature of 38°C. All determinations were performed at this temperature. The blood sample was injected from the tuberculin syringe, after removing the needle, into the micro condenser-type glass electrode through the top end of the electrode. Ten minutes were allowed for temperature equilibration before readings were taken. The meter was calibrated before each sample and checked again afterwards with pH standard solution prepared from Coleman buffer tablets (7.40 pH ± 0.02 at 30°C.).

Plasma chloride was determined by the iodometric titration procedure of Van Slyke and Hiller.[32] Because the amount of plasma available was extremely limited, only 0.04 cc. of plasma was analyzed. Triplicate analyses were run. In order to insure correction for deviations in the volumes of the pipettes and as a further check on the reagents, a 100 mEq./l. chloride standard was simultaneously treated exactly as an unknown. One tenth Normal HCl prepared from constant boiling HCl according to Hulett and Bonner[33] was used as standard and also for the titration in the total base. Thus:

$$\frac{\text{cc. 0.01151 N thiosulfate used for the unknown}}{\text{cc. 0.01151 N thiosulfate used for the standard}} \times 100 = \text{mEq. chloride/l. plasma}$$

Total serum protein was determined on approximately 0.02 cc. plasma by the gradient tube method of Lowry and Hunter.[34] The standards used were the copper sulfate standards of Phillips, Van Slyke et al.[35]

Total base was done by the electrodialysis procedure of Keys[36] as modified by Tsao.[37]

Calculations: "R" represents the acid constituents of the blood not analysed in the study and includes sulfate, organic acids and phosphate. "R" was calculated by subtracting the sum of the acid fractions from the total base of the blood.

Statistics: All statistical analyses and correlations were done by the Statistical Research Laboratory, University of Michigan.

Results

Table 1 is a compilation of blood chemical findings at birth and subsequent 4, 8, 12 and 24 hour sampling of all full term infants in the study. For ease of reading, total serum protein is calculated both as milliequivalents and grams per cent.

pH (chart 1.)—Statistical analysis (chart 1) reveals a significant difference in both range and average of values obtained from the group of premature infants‡ as compared to the full term infants at birth, i.e., the "newborn" average is higher and values less scattered. This difference is significant at the 1% level, highly acceptable with biologic testing. This significant difference persists in regard to average values (to the 0.1% level) obtained with premature infants (all ages) and full term infants during the remainder of the first day of life. This statistical difference also holds true in regard to range of values between premature infants and full term groups C, D, E and F.

It is further noted that there is a significant change in pH values of the full term infant during the first day of life. No statistically valid difference in range values is

* Weber electric vacuum oven, small model, obtainable from Arthur Thomas Co., Philadelphia.

† Obtainable from Cambridge Instrument Company, Ossining, N.Y.

‡ It must be emphasized that the data concerning the premature infants are for all ages (to 2 mo.) and weights (to 2.3 kg.) and do not necessarily reflect the blood chemical picture during the first few hours of life. However, no correlation of age of premature infant and chemical values could be found in the original study.

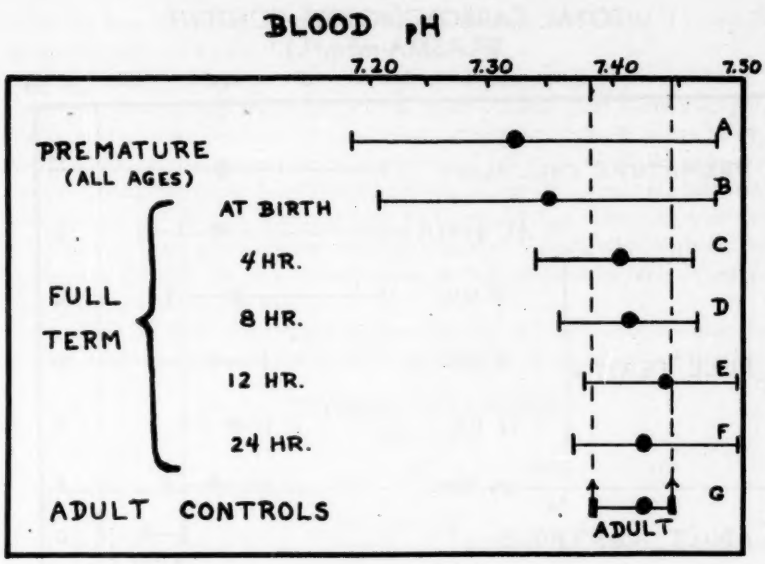

CHART 1

Comparison of average and range of values of blood pH, as found in premature infants, full term infants and adults. (Adult range is indicated by projected vertical lines.)

	No.	Range	Median	Standard Deviation	Groups Compared	P Median	P Variance
A Premature (all ages)	91	7.18-7.48	7.31	.065	A—B	.01	.01
B Full Term (birth)	43	7.20-7.48	7.34	.047	B—C	.001	.05
C Full Term (4 hr.)	10	7.33-7.46	7.40	.042	B—D	.001	.05
D Full Term (8 hr.)	11	7.35-7.46	7.41	.040	B—E	.001	.05
E Full Term (12 hr.)	10	7.37-7.50	7.44	.043	B—F	.001	.05
F Full Term (24 hr.)	12	7.36-7.50	7.43	.049	B—G	.001	.001
G Adult Controls	16	7.38-7.44	7.42	.019			

present except between full terms at birth (Group A) and the adult group. In other words by four hours of age the full term infant may well be expected to have a blood pH value within the adult range. This statement could not be made concerning a premature infant.

Carbon Dioxide Content (chart 2).—Full term infants, and to a more significant degree the premature infants, reveal a gross difference (greater range and lower average) both in average values and range of variation of carbon dioxide content of blood plasma when compared to the adult control group. Group size difference was eliminated statistically.

The difference in average values persists during the first day of life in the full term infant although the range of variation decreases to the point where it is not significantly greater than the range for adults.

Plasma Chlorides (chart 3).—The blood plasma chloride levels of newborn full term infants are less variable and not as high at birth or at any time during the first day of life as are the chloride levels for the group of premature infants. This difference is even more marked when both groups are compared to adults.

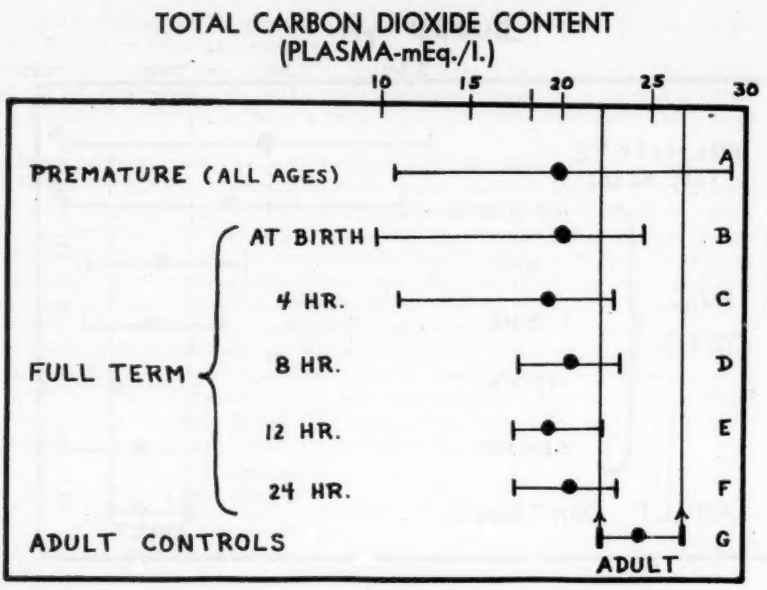

CHART 2

Comparison of range and average values of plasma carbon dioxide content as found in premature infants, full term infants and adults. (Adult range is indicated by projected vertical lines.)

	No.	Range	Median	Standard Deviation	Groups Compared	P Median	P Variance
A Premature (all ages)	73	10.9-29.1	20		G—B	.001	.01
B Full Term (birth)	43	11.2-24.5	20	2.8	G—C	.001	.01 p .05
C Full Term (4 hr.)	10	14.2-22.5	19	2.7	G—D	.001	.05
D Full Term (8 hr.)	11	16.0-22.4	21	1.7	G—E	.001	.05
E Full Term (12 hr.)	10	17.2-22.1	19	1.5	G—F		.01 p .05
F Full Term (24 hr.)	12	16.1-24.9	21	2.4	G—A		
G Adult Controls	16	21.4-26.4	24	1.4			

Normal full term infants at birth have a statistically significant higher average value for plasma chlorides than adults, but their range of variation is not significantly increased as is true of the premature infants. The apparent slight difference in chloride levels between full term infants any time during their first day and adults is significant statistically although not to the degree shown by the group of premature infants.

Total Base (chart 4).—There is a striking difference in the range of values obtained in the premature group as compared to all other groups. This difference is borne out statistically as noted in columns 5 and 6 of chart 4.

There is no statistical difference between the mean of the adult control group and full term infants at birth or at any time subsequent to birth except incidentally at four hours of age. In other words, by statistically eliminating the group size difference between the adult control group and the full term infants no significant difference in range or average value for plasma total base is detected between these groups. However, the premature infants have a significantly greater range of values and higher average (159

mEq./l.) than the group of newborn infants (average—153 mEq./l.) and the adult group (average—154 mEq./l.).

Total Serum Protein (chart 5).—As with other components of the "acid-base" picture there is a greater range of values of total serum proteins (and lower average) in premature infants than in either full term infants at birth or adults. It cannot be overlooked that the average total serum value of the group of full term infants decreases from birth steadily throughout the first day. The significance of this, if any, has not been ascertained. The average of full term infants at birth (6.12 gm./100 cc.) compares well with determinations made on cord blood by other investigators[18–20] using other methods, and results throughout the first day fit as a compromise to data obtained by other investigators[21–23] during the first two days of life.

"R" Fraction (chart 6).—Chart 6 represents the "R" fraction of the acid component of the "Gamble-diagram" after the CO_2 content, plasma chlorides and total serum pro-

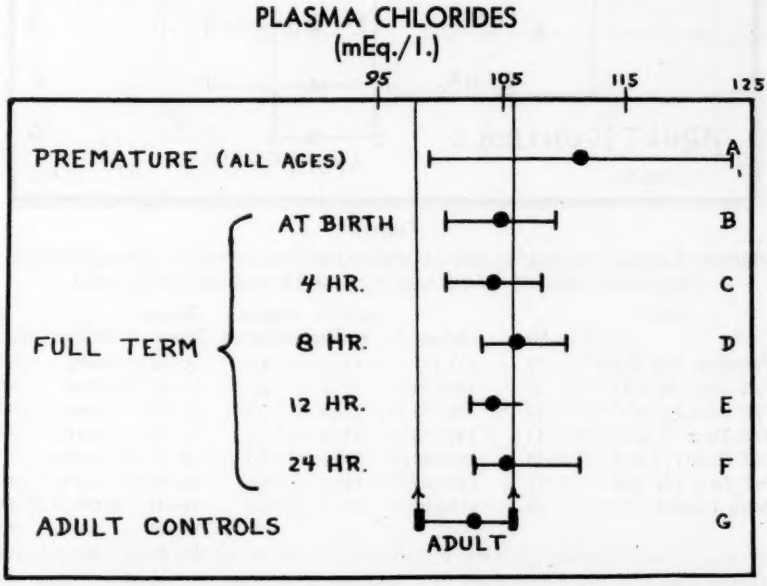

CHART 3

Comparison of average and range of values of plasma chlorides, as found in premature infants, full term infants and adults. (Adult range is indicated by projected vertical lines.)

	No.	Range	Median	Standard Deviation	Groups Compared	P Median	P Variance
A Premature (all ages)	73	99-124	111.5	5.1	A—B	.001	.001
B Full Term (birth)	43	100-109	104.5	2.6	A—C	.001	.05
C Full Term (4 hr.)	10	100-108	103.9	2.5	A—D	.001	.01
D Full Term (8 hr.)	11	103-110	106.1	2.2	A—E	.001	.001
E Full Term (12 hr.)	10	102-106	104.5	1.4	A—F	.001	.05
F Full Term (24 hr.)	12	102-111	105.3	3.2	G—B	.01	.05
G Adult Controls	16	98-105	102.4	2.4	G—D	.001	.05
					G—E	.02	.05
					G—F	.02	.05

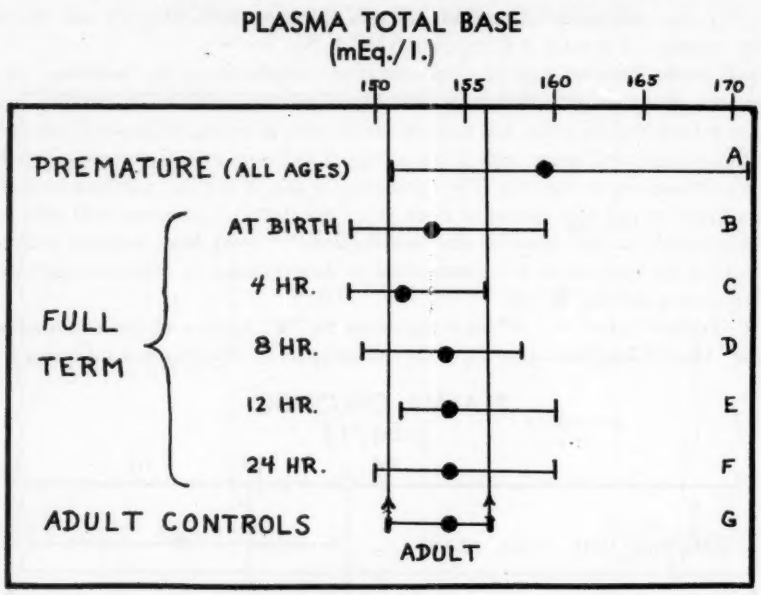

CHART 4

Comparison of average and range of values of plasma total base, as found in premature infants, full term infants and adults. (Adult range is indicated by projected vertical lines.)

	No.	Range	Median	Standard Deviation	Groups Compared	P Median	P Variance
A Premature (all ages)	73	152-171	159.2	4.0	A—B	.001	.01
B Full Term (birth)	43	148-159	153.1	2.7	A—C	.001	.05
C Full Term (4 hr.)	10	148-156	151.6	2.6	A—D	.001	.05
D Full Term (8 hr.)	11	149-158	154.0	2.7	A—E	.001	.05
E Full Term (12 hr.)	10	152-160	153.9	2.5	A—F	.001	.05
F Full Term (24 hr.)	12	147-160	153.6	3.6	G—B	.10	.05
G Adult Controls	16	152-156	154.3	1.6	G—D	.70	.05
					G—E	.60	.05
					G—F	.40	.01

teins have been subtracted from the total base. This, then, represents primarily phosphates, sulfates and other organic acids.

Again, as in other fractions of the acid component, the "R" value is much more variable in the "premature" group than in full term infants at birth or at any time subsequently during the first day of life. The average "R" value, however, is essentially the same for the premature infant (all ages and weights) as for the normal newborn during the first day of life, but is significantly higher than results obtained in the adult control group. Note the persistent narrowing of range of values (chart 6) as the adult group is approached.

It will be noted from the data presented that 46% (19) of the newborn infants studied had a significant rise in blood pH to adult levels during the first day of life with an increase in total blood carbon dioxide content. Only one third of the group

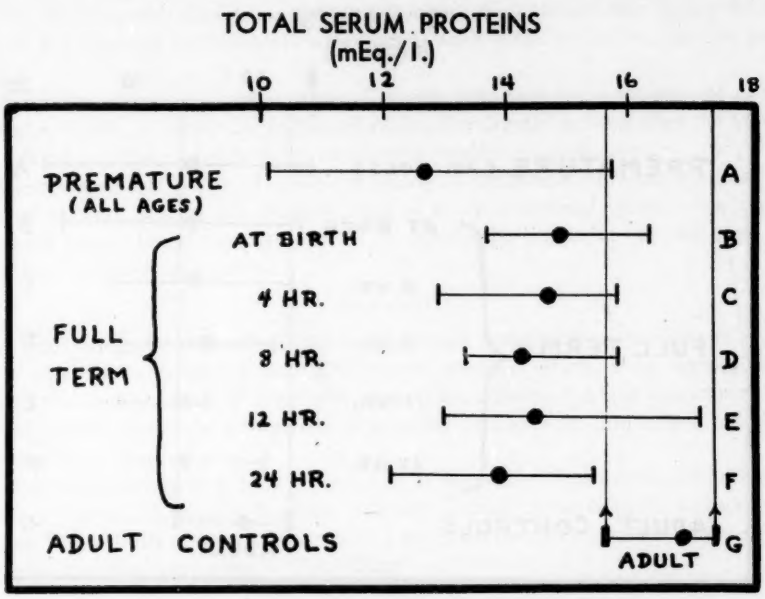

CHART 5

Comparison of average and range of values of total serum proteins as found in premature infants, full term infants and adults. (Adult range is indicated by projected vertical lines.)

	AVERAGE		RANGE	
	gm./100 cc.	mEq./l.	gm./100 cc.	mEq./l.
A Premature (all ages)	5.21	12.7	4.10-6.51	10.0-15.7
B Full Term (birth)	6.12	14.9	5.66-6.69	13.7-16.3
C Full Term (4 hr.)	6.04	14.7	5.32-6.52	12.9-15.8
D Full Term (8 hr.)	5.89	14.3	5.49-6.52	13.3-15.8
E Full Term (12 hr.)	5.98	14.5	5.32-7.03	12.9-17.1
F Full Term (24 hr.)	5.71	13.9	4.97-6.34	12.1-15.4
G Adult Controls	7.00	17.0	6.46-7.16	15.7-17.4

attained adult blood pH levels with a concomitant lowering of the blood CO_2 level; in other words, established equilibrium through the mechanisms of increased pulmonary ventilation. Twenty per cent of the total group[9] were unclassified in this respect, either accomplishing a rise in pH without a change in the blood CO_2 or revealing no significant changes in blood pH. Further studies are being planned in an attempt to correlate these findings with possible changes of oxygen saturation and carbon dioxide tension in capillary blood.

When one considers the consistent blood chloride and the total base values, it would appear that all newborn full term infants studied perhaps have at birth a greater renal "homeostasis" than a constancy of the respiratory system.

Further studies of urine produced during the first few hours of life may clarify some of the inconsistencies just noted. Certainly, there are indications that full term infants,[24] although only transiently, may possess and excrete organic acids in their efforts toward adult equilibrium. Further work is being planned in this respect.

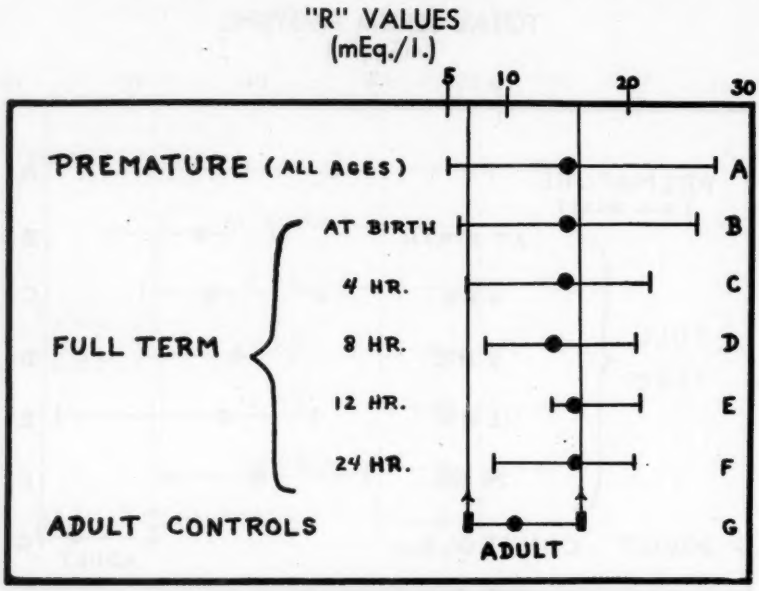

CHART 6

Comparison of average and range of values of plasma "R" fraction as found in premature infants, full term infants and adults. (Adult range is indicated by projected vertical lines.)

	No.	Ave.	Range Spread (mEq./l.)
A Premature (all ages)	73	15	5-27
B Full Term (birth)	43	15½	6-26
C Full Term (4 hr.)	10	15	7-22
D Full Term (8 hr.)	11	14	8-21
E Full Term (12 hr.)	11	16	14-21
F Full Term (24 hr.)	11	16	9-21
G Adult Controls	23	11	7-16

CONCLUSIONS

Average blood pH values for full term infants at birth are much the same as for a group of premature infants up to 2 months of age, although the extreme range of values is not as great.

Most full term infants have a blood pH within the adult range at least by the fourth hour of life.

The plasma chloride values for a group of premature infants were unpredictable (with a high average) as compared to values obtained in normal newborn infants. The latter, at birth, have plasma chloride levels which are comparable to adult values with respect to both range and average.

The plasma carbon dioxide content of full term infants at birth, as well as of most premature infants under 2 months of age, is significantly lower than the range of values obtained from adults and older children, and together with a lowered pH results in most instances in a picture of metabolic acidosis.

The plasma carbon dioxide content of full term infants remains low during the first day of life although the blood pH is within the adult range within the first few hours of life.

The range, as well as average value, of plasma total base (total cations) of normal newborn infants is comparable to that of adults. The average is lower than the average for premature infants and the range of values is significantly compressed.

The average value for "R" fraction (of anions) is the same for premature infants and normal newborn infants, and the total range of values is strikingly greater than that of the adult group. The average value of "R" is significantly higher for both full term and premature infants than for adults.

Summary

A study was made of the development of chemical homeostasis in the newborn infant. In a series of 43 essentially healthy, full term, newborn infants, serial determinations during the first day of life of blood pH, plasma CO_2, chloride and total base content, and serum protein were made. Comparison with similar data on premature infants and adults is presented.

Most full term infants at birth are in a state of metabolic acidosis with a lowered blood pH and plasma CO_2 content, but have essentially normal plasma chlorides and total base values. The majority of these infants within a few hours have a blood pH of adult level but maintain for some time a lowered CO_2 content.

Acknowledgments

This study would not have been possible without the fine cooperation of Dr. Norman F. Miller, Professor of Obstetrics and Gynecology, and Dr. Reynold L. Haas and other members of the staff of the Department of Obstetrics, University Hospital. Acknowledgment is particularly due Miss Hazel M. Avery, Supervisor of Obstetrical Nursing, and other members of her nursing staff.

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SPANISH ABSTRACT

Desarrollo de la Homeostasia Electrolítica Neonatal

Los autores realizaron un estudio comparativo de las concentraciones de los siguientes factores en la sangre capilar de recién nacidos obtenida durante el primer día de nacido: pH de la sangre, CO_2 del plasma, cloruro, Bases totales, proteínas totales del suero, y mediante substracción, el componente "R" del "diagrama de Gamble."

Los valores obtenidos de este grupo fueron comparados con los de un grupo de prematuros previamente reportado y además comparado con un grupo de adultos normales usado como control.

La mayoría de los niños a término presentaban al nacer un estado de acidosis metabólica con disminución del pH de la sangre y CO_2 del plasma, pero con valores normales de cloruros y bases totales del plasma. En la mayoría de los niños nacidos a término, el pH de la sangre subió en pocas horas a los valores adultos, pero el CO_2 del plasma se mantuvo bajo por algún tiempo.

Se determinó el contenido de O_2 de la sangre, y su capacidad y porcentaje de saturación, comparándose estos valores en distintos métodos de anestesia durante el parto. No hubo diferencias grandes en la saturación de O_2 cuando los distintos métodos fueron comparados, ni al momento del nacimiento, ni durante el primer día de vida.

University Hospital, University of Michigan

INDWELLING POLYETHYLENE NASOGASTRIC TUBE FOR FEEDING PREMATURE INFANTS

By STEPHEN ROYCE,* M.D., CLIFFORD TEPPER, M.D., WILLIAM WATSON, M.D., AND RICHARD DAY, M.D.
New York City

THIS communication describes an experience over a six month period with an indwelling nasogastric tube for feeding small premature infants. Heretofore in this hospital, infants too weak to suck well have been fed by gavage or with a dropper. Neither method is free of fault. The indwelling nasogastric tube represents an improvement over both these devices, since it permits an increase in the frequency of feedings without a concomitant increase in fatigue or in the likelihood of esophageal irritation. Feedings with this technic demand less skill of the nurse.

TECHNIC

Polyethylene† medical tubing is used with an internal diameter of 0.05 cm. and a length of about 22 cm. for the average premature infant. This material is not chemically irritating and, since the tube is slender and flexible, mechanical irritation is slight. The leading end of the tube is cut square, and smoothed with fine emery paper. Tubes of larger diameter are unnecessary and may be dangerous. The authors have heard of 2 instances of gastric perforation from their use.

Sterilization is accomplished by 2 min. of boiling, a process which shortens the tube about 25% and enlarges its diameter slightly. The tube may be kept from curling during boiling by threading it into a suitable length of glass tubing plugged at each end with gauze.

The nasogastric tube is inserted through the nose until it is estimated by rough measurement to have entered the stomach. The protruding 3.8 cm. are secured to the face with a generous amount of adhesive tape in such a manner as to cover the tube completely, making it difficult for the infant to hook his finger under it and pull it out.

The following criteria are used to indicate that the tube has not entered the trachea: 1. The infant tolerates the tube without respiratory difficulty. 2. With the bell of a stethoscope over the stomach area, air injected with a syringe can be heard to bubble into the stomach. 3. A quarter of a cc. of saline can be injected without causing respiratory disturbance. No instance of insertion into the trachea has so far been encountered.

In the infants reported upon here, feedings were started during the 2nd 24 hr. after birth.‡ First feedings were of glucose solution, succeeded later by a formula. Early feedings varied in volume from 4 to 10 cc. The feedings varied in volume from 4 to 10 cc. The interval between feedings varied from 1 to 3 hr. Nearly all the infants required parenteral fluid during the first week or 10 days.

The formula is injected by syringe, connection with the tube being made with a 23 gauge needle. Moderate force is necessary to push the average milk preparation through such a needle. To prevent the tube from becoming plugged with dried milk, it should be washed through after each feeding with 0.1 cc. of saline. The open end should be closed with a tapered sliver of wood.

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† Polyethylene is likely to be contaminated with a plasticizer which is irritating. Polyethylene prepared especially for medical use was obtained from Anchor Plastics, Inc., 533 Canal Street, New York City.

‡ Since infants dying in the 1st 24 hr. are not included, the mortality reported is better than the general nursery mortality.

Since feeding can be accomplished with little disturbance—often without waking the baby—the intervals between feedings may be shortened and the quantity given each time decreased to avoid overdistending the stomach. A continuous drip could be used if indicated. When the infant grows strong enough to try an occasional nipple feeding, the tube need not be removed. In this way a gradual shift to nipple feedings may be made.

Results and Complications

Thirty infants have been fed by the described technic. Ten weighed less than 1,000 gm. at birth, 16 weighed 1,000 to 1,499 and 4 weighed 1,500 to 1,800 gm. Twenty-eight of the 30 survived, including 9 of those under 1,000 grams in weight at birth. Feeding by nasogastric tube was continued in the different infants for periods varying from 7 to 49 days. The tube was changed occasionally, and shifted to the other nostril, and occasionally an infant pulled his tube out. The average period between such changes was 7½ days. A total of 540 tube-days has elapsed during the study.

The two infants who died were autopsied. One of these had a massive brain hemorrhage and the other probable septicemia. In each, there was an esophageal ulcer. The ulcers were about 1 cm. in diameter. They were shallow, and were situated in the upper, anterior part of the esophagus. Similar ulcers have been found at autopsy by Gruenwald and Marsh[1] in 16⅔% of 310 infants. Their data do not indicate the frequency of such ulcers in premature infants. In the cases presented here, the role, if any, played by the nasogastric tube in the genesis of the ulcers could not be determined. Esophagitis, such as that described by Ebbs,[2] was not present. Thrush did not appear in any of the infants being fed by the polyethylene tube. Crusting or bleeding around the tube was never noted. Occult blood was searched for in the stools of 18 of the infants on 50 occasions. In no instance was a positive guaiac test obtained.

In two infants, purulent rhinitis, limited to the side of the tube, developed. In both, Staph. aureus hemolyticus was cultured from the discharge. The first was in a 760 gm. infant, who had seven other purulent infections before and after the tube was removed. These infections involved the middle ears, eyes, skin and umbilicus. The second case was in a larger infant who had two other infections, all caused by the same organism. In both infants, the rhinitis subsided shortly after removal of the tube and the institution of antibiotic therapy.

In no other infants was there evidence of nasal irritation.

Summary and Conclusions

Experiences with an indwelling polyethylene nasogastric tube in feeding 30 small premature infants for periods varying from 7 to 49 days have been described. The technic has the following advantages: 1. The interval between feedings may be shortened, if necessary, without any increase in the likelihood of esophageal irritation. 2. Feedings disturb the infant so little as to cause no fatigue. 3. Feeding can be accomplished so easily that less skill is demanded of the nurse.

Two of the 30 infants died, and each had an ulcer in the upper, anterior part of the esophagus. Similar ulcers were noted by Gruenwald and Marsh[1] in 16⅔% of 310 autopsied infants. Two other infants developed a purulent rhinitis on the side of the tube. Each infant suffered from other, seemingly unrelated infections at the time. Thrush was never noted. Occult blood was absent in the 50 stools obtained from 18 infants, as indicated by a negative guaiac test.

Nine of the 10 infants weighing less than 1,000 gm. at birth survived, as did 15 of the 16 who weighed 1,000 to 1,499 gm.

A complete evaluation of esophageal irritation in tube as compared with gavage feeding will require a more extended study.

Results so far with the polyethylene tube lead the authors to believe it to be a better device for feeding premature infants than either the rubber gavage tube repeatedly inserted or the dropper.

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Spanish Abstract

Sonda Permanente Nasogastrica de "Polyethylene" en la Alimentación de Niños Prematuros

Las experiencias usando una sonda permanente nasogastrica de "polyethylene" en la alimentación de niños prematuros por periodos variables de 7 a 49 dias son descritas. Esta tecnica tiene la ventaja que las alimentaciones molestan al niño muy poco y asi los intervalos de alimentación pueden acortarse sin producir fatiga como ocurre con el uso de goteros, ó causar irritación del esofago como ocurre con el uso de sondajes repetidos. La retención de la sonda durante un promedio de siete y medio dias, solo causó una pequeña irritacion del esofago. Dos niños los cuales sufrian de infecciones, desarrollaron una rinitis purulenta en el lado que tenian la sonda y uno de ellos desarrolló una otitís media de corta duración. La autopsia de dos niños demonstró la presencia de una pequeña ulcera del esofago en cada uno. Estas ulceras del esofago han sido descritas por Gruenwald en un 16% de todos prematuros examinados en la autopsia. Si la incidencia de esta ulcera se aumenta o disminuye con el metodo descrito, queda para ser determinado en el futuro. La experiencia clinica por el momento presente parece indicar que este metodo es preferible al uso repetido de sondas o la alimentación con gotero de niños prematuros, especialmente aquellos pesando menos de 1200 gramos.

622 West 168th Street

SOURCE OF ERROR IN TEST FOR STOOL TRYPSIN

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THE development of a method utilizing the stool to evaluate trypsin activity in patients suspected of having mucoviscidosis (pancreatic fibrosis) was recently described by Shwachman et al.[1] Such a procedure can be fully appreciated only by those who have spent several hours unsuccessfully attempting to obtain an adequate specimen of duodenal fluid. The stool technic is simple and requires little time, yet in infants has a high degree of accuracy. Trypsin was demonstrated in the stools of 100% of premature infants and 95.7% of infants under 2 years of age who did not have mucoviscidosis. It is the purpose of this paper to report variable results using different brands of gelatin film.

Since the test for stool trypsin was described, it has been very popular with the house staff at Children's Hospital where each resident performs his own tests. Dental film, 2″ × 3″ (Eastman Kodak), was originally selected as being the most convenient size for the test. While this was used there was no variation in the results obtained with three stool specimens from each patient. Recently several patients, who clinically had mucoviscidosis, were found to have stools which in 1 to 5 and 1 to 10 dilutions digested the gelatin coating of the film. Stools from healthy babies and sterile distilled water were used as controls and it was discovered that after incubation for 1 hour at 37° C. even the distilled water digested the gelatin. It was then determined that the supply of dental films had been exhausted and that larger films were being sectioned to supply the convenient smaller size. It was further determined that there were two brands of film available in the hospital: (a) Kodak made by Eastman Kodak and the source of all the dental films, and (b) DuPont film made by E. I. DuPont de Nemours & Co.

Using stools from 5 infants with proved mucoviscidosis and 21 others who were not ill, it was demonstrated that the two types of film gave different reactions which were consistent for the type of film as well as the clinical diagnosis except in one instance. When Kodak film was used and incubated for one hour at 37° C. or left at room temperature for two hours, there was no digestion of gelatin by stools from proved cases of mucoviscidosis. Stools from healthy infants digested the gelatin in both 1 to 5 and 1 to 10 dilutions, while in no case did the distilled water affect it. When DuPont film was used and incubated at 37° C. for one hour, not only was the gelatin digested by stools from healthy infants, but also by stools from the patients with mucoviscidosis as well as by distilled water. At room temperature for two hours, the DuPont film gave results identical with those obtained by using Kodak film under similar conditions or at 37° C. for one hour. When Kodak film was incubated at 37° C. for two hours, however, the stool from a patient with mucoviscidosis digested the gelatin in both 1 to 5 and 1 to 10 dilutions (table 1).

The expiration dates for both types of film were approximately the same, one year hence, and all stools were tested within four hours.

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TABLE 1

STOOL TRYPSIN

Source of Specimens	Procedure	Kodak Film			DuPont Film		
		Stool (1:5 dil.)	Stool (1:10 dil.)	Water	Stool (1:5 dil.)	Stool (1:10 dil.)	Water
5 infants with mucoviscidosis	37° C. 1 hr. (5 infants)	0	0	0	+	+	+
	Room 2 hr. (5 infants)	0	0	0	0	0	0
	37° C. 2 hr. (4 infants)	0	0	0	+	+	+
	37° C. 2 hr. (1 infant)	+	+	0	+	+	+
21 healthy infants	37° C. 1 hr.	+	+	0	+	+	+
	Room 2 hr.	+	+	0	+	+	0

+ Digestion of gelatin.
0 No digestion of gelatin.

DISCUSSION

The gelatin film test for stool trypsin has a high degree of reliability and has been recommended as an office test, although incubation for one hour as 37° C. is to be preferred.[1]

It would seem that in most cases in which the physician wishes a test for stool trypsin on an outpatient, he will take the stool to the hospital and request that the test be performed, in which case incubation will be used. In hospitals using DuPont film, the results will not be reliable since all will show digestion of gelatin after incubation.

If the test is done as an office procedure at room temperature, identical results will be obtained with Kodak and DuPont film.

SUMMARY AND CONCLUSIONS

A source of error in the gelatin film test for stool trypsin is reported. Identical results are obtained with Kodak and DuPont film when incubation at room temperature for two hours is used.

The gelatin on DuPont film incubated at 37° C. for one hour is digested by stools from infants with mucoviscidosis and also by distilled water as well as by stools from healthy infants. Stools from some infants with mucoviscidosis will digest the gelatin on Kodak film when incubated at 37° C. for two hours.

Kodak film should be used if the preparations are to be incubated at 37° C. for one hour, as recommended in the original description of the technic.

REFERENCE

1. Shwachman, H., Patterson, P. R., and Laguna, J., Studies in pancreatic fibrosis: Simple diagnostic gelatin film test for stool trypsin, PEDIATRICS 4:222, 1949.

SPANISH ABSTRACT

Causa de Error en la Determinación de la Tripsina Fecal

El autor señala una causa de error en la determinación de la tripsina fecal usando el metodo de la placa de gelatina (gelatin film test). Los resultados de la prueba fueron similares con el uso de placas radiograficas Kodak y Dupont cuando estas son incubadas a la temperatura del curato por dos horas.

Se observó que la gelatina de las Dupont incubadas a 37 grados Centigrados por una hora, es digerida por las heces fecales de niños con mucoviscidosis, así como tambien por agua destilada y por heces fecales de niños normales. La gelatina de las placas Kodak incubadas a 37 grados Centigrados por dos horas, es digerida por las heces fecales de niños con mucoviscidosis.

El autor sugiere el uso de placas Kodak cuando las muestras fecales son incubadas a 37 grados Centrigrados por una hora, como es recommendado en la técnica original de este metodo.

125 DeSoto Street

ENCEPHALITIS COMPLICATING ATTENUATED RUBEOLA

Report of a Case

By JOSEPH L. ROSENZWEIG, M.D., AND WALTER G. KLUGH, M.D.
Hot Springs, Ark.

A REVIEW of the literature fails to reveal any definite case of encephalitis following attenuated rubeola similar to the case reported here. Holliday[1] refers to two possible instances but in neither could a definite diagnosis be made. Janeway[2] mentions one case of mild encephalitis with recovery in a child who had received concentrated human gamma globulin, but the patient obtained no benefit from the drug and experienced an average case of rubeola. Complications of modified rubeola appear to be infrequent.[2-4] Anderson and Ket[4] reported on 46 cases in which there were no complications. Stillerman, Marks and Thalhimer[3] observed complications in 1.0% of 502 patients who had received prophylactic convalescent serum. Janeway[2] mentions an incidence of 0.4% where the use of concentrated human serum gamma globulin had resulted in a modified form of the disease, whereas those patients who failed to show any modification had complications in 5.5%.

CASE REPORT

D. G., a 3 yr. old white female, was admitted to the hospital with the complaint of recurrent convulsions for 1½ hr. History prior to 1 mo. before admission had been entirely negative, but at that time she had a mild case of varicella which lasted only a few days. Twenty days before admission, her 7 yr. old sister developed a slight cough and oral temperature of 37.7°C. These symptoms became progressively worse and 2 days later she had Koplik spots and an early morbilliform rash; a diagnosis of rubeola was made (W. G. K.). This child went on to have a fairly severe case of rubeola.

Four days after the original exposure to her sister, the patient (15.9 kg.) was given 2.0 cc. of human immune serum globulin with the purpose of attenuating her probable infection. The amount usually recommended was exceeded due to the severity of the rubeola in this area at that time. Record was not kept of the exact product used, but it was from one of the widely recognized pharmaceutical companies. The child was asymptomatic until 10 days later when the family noticed she seemed to lack some of her usual vigor. The following day her oral temperature was 37.7°C., and the parents found "spots in her mouth" (Koplik spots had been pointed out to the parents when present in the older sibling). She had practically no cough or coryza. Aspirin, 0.165 gm., was begun and continued every 3 hr. during the illness. Twelve days after the original exposure she was "completely broken out" with "tiny red bumps." The family described these as being widely distributed, but "not as puffed or swollen" as those the sister had had. On the 13th day the temperature was 37.7°C. and the rash persisted, but the next day the rash was fading and the fever had subsided; however, the patient was still receiving aspirin. At no time had she seemed to feel very bad. On the 15th day after exposure the temperature returned to 37.7°C. At 2:30 a.m. the next day, the mother noticed that the temperature had risen and gave another dose of aspirin. At 3:00 a.m. the family was awakened by a "sucking and chewing" noise. They found the patient having a generalized convulsive seizure. Alcohol sponges and a tepid enema failed to relieve the symptoms, and she was taken to the hospital. In the interim the original seizure ceased and was followed by intermittent attacks of varying duration.

On admission to the hospital the axillary temperature was 38.3°C., pulse, 120, and respirations were 22 to 28. Examination revealed a well nourished and hydrated child with a vacant stare and mild circumoral cyanosis though she was in an oxygen tent. She was comatose, and had frequent

From the St. Joseph's Infirmary, Hot Springs, Ark.
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grinding motions of the jaw and twitchings of the lips. Intermittent generalized convulsions recurred, with the right lower extremity showing the maximum motion. A faint, generalized, maculopapular eruption was present on the body and extremities. The remainder of the examination was within normal limits with the exception of slightly dilated pupils and a lateral nystagmus with the fast component to the right; mild nuchal rigidity; and moderate increase in the right patellar reflex.

After controlling the convulsions with chloral hydrate given rectally, further diagnostic studies revealed the following results: Hgb. 13.7 gm./100 cc.; RBC 3.5 million/cm. and WBC 11.9 thousand/cmm. with 75% polymorphonuclears and 25% small lymphocytes. Lumbar puncture disclosed a faintly hazy fluid under no increased pressure. There were 176 cells/cmm. Stained smears showed 95% to be lymphocytes and 5% polymorphonuclears. No organisms were found and the culture produced no growth. Spinal fluid sugar was 83 mg./100 cc. and spinal fluid protein totaled 22 mg./100 cc.

The patient received chloral hydrate rectally for the control of convulsions, and 300,000 units of procaine penicillin daily as prophylaxis against secondary invading organisms. On the afternoon of the day of admission 500 cc. of 5% dextrose in distilled water was given by slow drip into the thighs. She had no convulsions after midnight of that day. By noon of the following day she had begun to talk, but her conversation was vague. The right patellar reflex had returned to normal, the nystagmus had ceased, and no new pathologic findings could be found. The temperature returned to normal on the 2nd hospital day and her speech was definitely more coherent. Her worst mental cloudiness was associated with her inability to understand and adjust to her hospital surroundings. For this reason, she was sent home with special nurses on 24 hr. duty. Within a few hours after arriving home she was talking coherently and seemed quite happy. Her improvement was rapid from this time on and the nurses were discontinued after 24 hr.' service in the home. The patient was seen last on the 7th day after discharge from the hospital. At that time, the only points of interest were a shyness and fairly frequent nail biting, neither of which had been present prior to the illness. The family left town soon after that visit, but the father has written that within 1 mo. after discharge the shyness and nail biting had both ceased.

Comment

At the present, concentrated human serum gamma globulin is the material of choice in the prevention and modification of rubeola.[2,5] While the incidence of complications following attenuation is low, as indicated, the case reported here should serve to make us feel less complacent regarding the possibility of the occurrence of a serious complication. As a complication of ordinary rubeola, encephalitis seems to be becoming more frequent[6] or else is being reported more accurately. The highest incidence found is once in every 642 cases.[6] In the patient reported here undoubtedly the relatively low temperature was influenced by the regular administration of an antipyretic and she was not seen by a physician during the uncomplicated course of her illness. However, the length of the incubation period, the lack of malaise or prostration, and the almost complete absence of cough and coryza certainly indicate, retrospectively, that the child's illness was modified.

Encephalitis does occur after relatively mild cases of unmodified rubeola, and there is no real reason to believe that such a complication should not follow those made milder by the use of immune serum globulin. Nevertheless, it is interesting to speculate as to the relationship between severity of infection and the frequency of encephalitis. The question should be raised as to whether the decrease in complications following modification of the disease includes a lowering in the incidence of post rubeola encephalitis. With the increasingly widespread use of prophylactic immune serum globulin, it is likely that in the near future there will be sufficient data available for adequate evaluation. It is hoped that this report may stimulate more interest in this subject.

Summary

A case of encephalitis with probable complete recovery following modified rubeola is reported. It is suggested that the occurrence of similar cases be recorded.

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Spanish Abstract

Encefalitis Complicando un Caso de Rubeola Atenuada (Sarampion)

Se presenta un caso de rubeola atenuada complicada con una encefalitis. Se estima que este caso es el primero publicado en la literatura médica. Los autores sugieren el reporte de casos similares para asi poder evaluar mejor las ventajas actuales inherentes al uso de inmuno-sero-globulina humana.

126 Hawthorne Street

JUVENILE PERNICIOUS ANEMIA

By EDWARD H. REISNER, JR., M.D., JAMES A. WOLFF, M.D., R. JAMES MCKAY, JR.,* M.D., AND EUGENIA F. DOYLE, M.D.
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THE macrocytic anemias associated with megaloblastic bone marrows are deficiency states which can develop as a result of several different mechanisms. That resulting from failure of absorption of vitamin B_{12} due to lack of the intrinsic factor of Castle, present in normal gastric juice, is known as Addisonian pernicious anemia. The peak incidence of this disease is in the sixth decade, and it is ordinarily associated with histamine refractory achlorhydria. The disease has seldom been described in childhood, and when the criterion of absence of hydrochloric acid after histamine is insisted upon, the number of acceptable reported cases in the literature is only seven. It is the authors' belief, however, that intrinsic factor deficiency may occur without achlorhydria, and this paper presents the histories of four children who are believed to be examples of true pernicious anemia, although three of them lack that finding.

REVIEW OF THE LITERATURE

Peterson and Dunn[1, 2] in 1946 reviewed the literature relating to pernicious anemia in children, and reported a case which they felt was one of true pernicious anemia in a child. Their criteria were: macrocytic anemia; gastric achlorhydria resistant to histamine stimulation; arrest of bone marrow erythropoiesis at the megaloblastic level; reticulocytosis following specific therapy; and necessity of continued therapy to prevent relapse. On this basis they were able to find only one other case[3] classifiable as true pernicious anemia, and a third possible case,[4] the report of which was incomplete. Benjamin[5] subsequently reported a case in which the absence of intrinsic factor was proved despite inconstant achlorhydria.

The present investigators have reviewed 75 cases of pernicious or pernicious-like anemia in children, culled from the available world literature since 1927. On critical analysis the majority of these reported cases can be eliminated on grounds of insufficient study, inconclusive evidence or incorrect diagnosis. As a result of this review only 12 cases were found which seem to represent true Addisonian pernicious anemia in children. These are summarized in table 1, together with the four cases presented in this paper. Andreasen's case[4] was not included because a copy of the original report could not be obtained. An attempt was made to obtain a follow-up report on those cases in which pernicious anemia seemed possible or probable but in which no relapse was recorded in the original report. In this manner the cases of Adams and McQuarrie[6, 7] and of Eckman and Rowe[8, 9] were found not to be instances of pernicious anemia in that permanent cure was attained after

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one course of treatment with liver extract, while the converse was found in the cases of Kaplan and Bernard[10, 11] and W. P. Murphy.[12, 13]

Criteria for selection were: macrocytic anemia with megaloblastic bone marrow; exclusion of other causes of megaloblastic hematopoiesis; and necessity for continued specific therapy to prevent relapse. Pohl's[14] and W. P. Murphy's cases[12, 13] were included despite the lack of marrow studies because the evidence for pernicious anemia was felt to be otherwise convincing. Special mention should be made of the exclusion of Jonsson's[15] first patient. While true pernicious anemia was considered highly probable it seemed advisable to reject the case without biologic demonstration of the absence of intrinsic factor, because of the undoubted presence of celiac disease in early childhood.

While some authors[16] will not make a diagnosis of Addisonian pernicious anemia in the presence of free hydrochloric acid, the present authors hold the view of many current authorities[17] that the essential feature for the diagnosis is absence of intrinsic factor, which may occasionally occur without achlorhydria. In adults this is exceedingly rare. The only conclusive proof of the absence of intrinsic factor is the biologic test establishing the inability of the patient's gastric juice to promote the absorption of extrinsic factor. Askey[13] in 1944 reviewed published reports of 47 patients alleged to have pernicious anemia without achlorhydria. He concluded that 15 of these were possible cases, but that none of them were proved. His criteria required exclusion of all other possible causes of macrocytic anemia, biologic demonstration of the absence of intrinsic factor and response to specific therapy. Since the publication of Askey's paper, two cases have been reported that fulfilled his strict criteria, those of Benjamin[5] and A. Murphy.[19] It is of interest that Benjamin's case was a child and Murphy's a young adult of 23 years.

Case Histories

Case 1. (Figs. 1 and 2.) C. Z., was apparently normal until the age of 2 yr. when, following an attack of measles, her RBC count was found to be 1.8 million/cmm. with Hgb. 29 gm./100 cc. She was given 3 blood transfusions. At the age of 2 yr., 10 mo., RBC count was 1.1 million/cmm. and Hgb. 21 gm./100 cc. Three blood transfusions raised the blood level to 4.4 million/cmm. After 8 mo. the count had fallen to 3.1 million/cmm. with Hgb. 50 gm./100 cc., and she was given a blood transfusion and intramuscular vitamin B complex. Subsequently severe epistaxis began and the blood fell to 1.3 million/cmm. with Hgb. 16 gm./100 cc. so that she received 2 more transfusions. After 5 mo. she relapsed again and was given reticulogen®* 1 cc. intramuscularly daily for 9 days (an estimated dose of 180 U.S.P. units of antianemic substance). At the age of 6 yr., 9 mo., RBC count was 0.6 million/cmm. with Hgb. 15 gm./100 cc. Reticulogen® and liver extract were again given for 5 and 20 days, respectively, along with a single transfusion. One year later her count was down again to 0.6 million/cmm. with Hgb. 10 gm./100 cc. Two transfusions, liver extract (4 U.S.P. u.) twice weekly, as well as iron, Brewer's yeast and vitamin B complex by mouth and folic acid (folvron®,† 1 capsule thrice daily) induced a remission that lasted for 6 mo. Following an acute bronchitis RBC count fell to 0.9 million/cmm. and Hgb. 18 gm./100 cc. She was given 2 transfusions and unknown amounts of liver, iron and vitamin B complex.‡

Six months after this, at 8¾ yr. of age, the patient had again relapsed, with RBC 1.0 million/cmm.; Hgb. 7 gm./100 cc. and WBC 5.4 thousand/cmm. with normal differential. After 2 blood transfusions a bone marrow aspiration was done and reported to show erythroid hyperplasia

* Reticulogen® (Lilly) is refined liver extract, 1 cc. equivalent to 20 U.S.P. units.

† Folvron® (Lederle) contains 1.7 mg. folic acid and 194 mg. ferrous sulfate/capsule.

‡ During the 1st 6 yr. the patient was cared for during relapse in a small private hospital. Available data are incomplete, and complete blood studies were never attempted. No standard of reference for the hemoglobin percentages is available. Macrocytes were reported in several smears on different admissions.

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REPRESENTATIVE DATA IN JUVENILE PERNICIOUS ANEMIA IN 12 PA

Author	Age (When Diagnosis Was Made)	Sex	Hgb.	RBC (Millions)	M.C.V.	WBC	Blood Smear	Megaloblast Percentage in Marrow
Dedichen[9]	9/12	M	41%	2.12		10,000	Anisocytosis Poikilocytosis Some megaloblasts	
Pohl[14]	13	F	44%	1.5		5,600	Anisocytosis Poikilocytosis Polychromasia	"Megaloblastic"
Jonsson[15]	4	M	38%	1.75		5,000	Anisocytosis Poikilocytosis Polychromasia Nucleated RBC	"Megaloblastic"
Benjamin[5]	1 9/12	F	4.3 gm.	1.37		4,200	Anisocytosis Poikilocytosis Polychromasia Macrocytosis Megaloblasts	10.2 (During mild Relapse)
Peterson and Dunn[1-2]	2 7/12	F	6.8 gm.	1.47		7,800	Anisocytosis Poikilocytosis Nucleated RBC	21.0
Waagstein[45]	1 7/12	M	30%	0.90		7,600	Aniscytosis Poikilocytosis Macrocytosis "Macroblasts"	55.0
Davis *et al.*[46]	1 9/12	F	5.5 gm.	1.38		9,100		20.0
Murphy, W.P.[10-11]	10	F	56%	2.7		2,800	Macrocytosis Microcytosis Pear-shaped and tailed forms	Not Examined
Kaplan and Bernard[10-11]	2 6/12	F	20%	0.656		6,400	Macrocytosis Anisocytosis Poikilocytosis Polychromasia 1 Megaloblast/100 WBC	16
Kade[47]	14	M	35%	1.27		3,100	Anisocytosis Poikilocytosis Polymorphonuclear hypersegmentation	"Megaloblastic"
Hamilton and Fowler[48]	14	F	6.4 gm.	1.5	106	3,800	Anisocytosis and poikilocytosis	"Megaloblastic Hyperplasia"
Rosenzweig and Bruton[49]	4/12	F	7.9 gm.	2.63	99	3,100	Anisocytosis	16.6
C.Z. (Present Report)	9 6/12	F	6.5 gm.	1.48	124	5,100	Macrocytosis	55.0
V.Z. (Present Report)	8 3/12	F	6.1 gm.	1.38	130	7,000	Megaloblasts	60.0
J.M. (Present Report)	5 1/12	M	9.0 gm.	2.13	144	4,900	Anisocytosis Poikilocytosis Macrocytosis Polymorphonuclear hypersegmentation	78.0
B.M. (Present Report)	3 5/12	M	12.5 gm.	2.82		8,150	Anisocytosis Poikilocytosis Macrocytosis Polymorphonuclear hypersegmentation	"Megaloblastic"

BLE 1

TIENTS PREVIOUSLY REPORTED AND IN 4 SUBJECTS OF THIS REPORT

Reticulocyte Percentage (Before Treatment)	Reticulocyte Percentage (Peak After Treatment)	Free HCL	Tongue	Neurologic Findings	No. of Relapses	Family History
	14.0	Absent		None	2	Negative
1.0	36.0	Absent	Smooth	Tingling of hands and feet during 2nd relapse	2	Negative
1.0	22.0	Present	Smooth red	None	2	Grandfathers were cousins
2.0	42.0	Present	Atrophic	None	5	Older brother died at 2½ yr. of macrocytic anemia
0.5	19.0	Absent		None	4	Sibling died of diarrhea and anemia at 3 yr.
0.4	28.0	Present	Red	None	1	Parents were 1st cousins
1.8	35.0	Present		None	At least 3	Negative
		Absent		None	1	Mother subsequently developed pernicious anemia
	18.0	Present	Atrophic	None	2	Negative
1.0	22.0	Absent	Recurrent Glossitis	Tingling of hands	4	Negative
2.2	26.0	Absent	Atrophic	None	2	Mother had pernicious anemia and CNS changes
0.5	17.9	Absent	Atrophic	None	3	Negative
<0.1	26.0	Absent in relapse Present in remission	Marked Glossitis	Diminished vibratory sense in toes during relapse	11	Sibling of V.Z.
<0.1	16.4	Present	Marked Glossitis	None	2	Sibling of C.Z.
1.0	30.0	Present initially Later absent	Moderate Glossitis	Babinski signs present Persistent ataxia Mental retardation	4	Sibling of B.M. Grandfathers were 1st cousins
1.2	7.3	Absent	Slight Glossitis	Babinski signs equivocal Persistent ataxia Mental retardation	2	Sibling of J.M. Grandfathers were 1st cousins

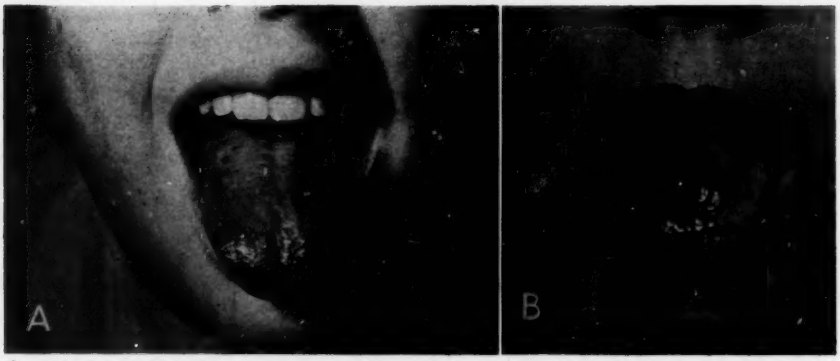

FIG. 1. A. Patient C. Z.: tongue 2 wk. after treatment with vitamin B_{12}.
B. Patient V. Z. (sibling of C. Z.): tongue before treatment.

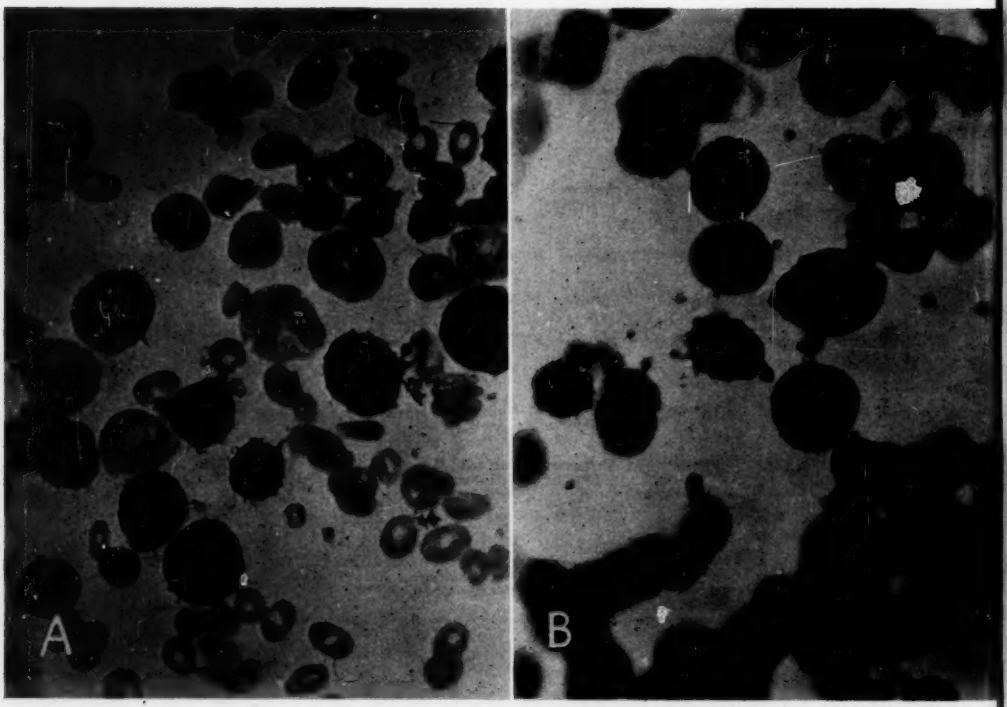

FIG. 2. Patient C. Z. A. Marrow before treatment. B. Marrow 18 days after treatment with vitamin B_{12}.

(megaloblasts 3%, erythroblasts 13%, normoblasts 35%). Unknown amounts of liver extract, iron and vitamin B complex were all given. RBC count rose to 3.7 million/cmm.

Once more she failed to return for treatment and after 3 mo. she developed her usual symptoms of weakness, anorexia and pallor and was admitted to Babies Hospital. RBC count was 1.4 million/cmm. with Hgb. 4.6 gm./100 cc. and WBC 4.8 thousand/cmm. with 44% lymphocytes. Serum bilirubin was 1.45 mg./100 cc., Van den Bergh indirect. Reticulocytes were 1.7%. The patient was transfused on admission. Ten days later reticulocytes were 10% and RBC 2.2 million/cmm. Another transfusion raised the count to 2.7 million/cmm. but in a few days it fell to 2.2 million/cmm. Gastric analysis revealed no free hydrochloric acid after histamine. A marrow examination showed normoblastic hyperplasia and active erythropoiesis. Parenteral liver extract was given, 4 U.S.P. u. daily from the 21st to the 39th hospital day, with maximal reticulocyte response of 5% on the 28th day. RBC rose to 3.6 million/cmm. Gastric analysis at this time revealed free hydrochloric acid.

Six months after this admission the patient and her siblings were placed in a foster home, where she remained well for 2 mo. and then developed a sore tongue. This subsided spontaneously after 3 wk., but she was admitted to the Pediatric Service of Bellevue Hospital for study 3 mo. later., at the age of 9 yr., 6 mo. On admission she appeared well developed and nourished, but listless and pale. The tongue was smooth and glistening with marked atrophy of papillae. There was a soft systolic murmur at the apex of the heart and the liver edge was felt just below the costal margin. Neurologic examination showed absent deep tendon reflexes in the lower extremities but no sensory or vibratory impairment. RBC count on admission was 2.6 million/cmm. with Hgb. 8.5 gm./100 cc.; mean cell volume 103 $c\mu$; reticulocytes 0.2%. On the 7th hospital day iron 0.6 gm./day was begun and increased to 1.2 gm. 4 days later. After 12 days of iron therapy the RBC count was 1.4 million/cmm., Hgb. 6.5 gm./100 cc.; WBC 5.1 thousand/cmm. with 40% neutrophiles and 58% lymphocytes; platelets 205,000 and reticulocytes 0.0%. A marrow aspiration showed megaloblastic hyperplasia with 19.6% promegaloblasts and 34.4% basophilic, hypochromatic and orthochromatic megaloblasts and many giant metamyelocytes.

Additional laboratory studies showed no free hydrochloric acid after histamine on 2 occasions; normal basal metabolic rate and serum cholesterol; normal gastrointestinal roentgenogram and stool fat content; no ova or parasites in 8 different stool examinations; normal urinary excretion levels of thiamine (55 μg./100 cc.) and riboflavin (2.7 μg./100 cc.); normal levels of serum albumin and globulin, prothrombin, cholesterol esters; slightly positive cephalin flocculation; thymol turbidity of 11 McLaglen units; and 30% retention of bromsulphonphthalein after 45 min.

On the 20th hospital day vitamin B_{12} 10 μg. were injected intravenously. Within 72 hr. there was a marked subjective improvement and reticulocytosis had begun. The reticulocyte peak of 26% was reached on the 6th day after treatment and 2 days later the RBC count was 3.0 million/cmm. and the WBC 13.0 thousand/cmm. with 64% neutrophiles. On the 35th day the patient complained of soreness of the tongue, which was bright red and atrophic at the tip and margins. Three days later RBC count was 2.7 million/cmm. At this time vitamin B_{12} 12.5 μg. were given intramuscularly. In 3 days the subjective and objective signs of glossitis had disappeared (Fig. 1A). A week after the last injection an additional 25 μg. of vitamin B_{12} was given intramuscularly, following which the RBC count rose to 3.7 million/cmm. on the 57th hospital day. Two months later with no further therapy the RBC count was 4.2 million/cmm. with Hgb. 14.0 gm./100 cc.

After the blood count was restored to normal levels gastric analyses showed free hydrochloric acid present without histamine stimulation on repeated occasions. The cephalin flocculation, thymol turbidity and bromsulphonphthalein excretion tests were also normal at this time. The bone marrow showed normoblastic hyperplasia.

Sufficient gastric juice was collected from the patient to perform a Reimann test[20] for intrinsic factor. Twenty cubic centimeters of gastric juice were incubated with 20 gm. of liver each day, and the mixture was fed without effect for 10 days to an adult patient with known pernicious anemia who subsequently responded to parenteral vitamin B_{12}.

Treatment was discontinued to permit further study on C. Z. Three months after last admission RBC count was 2.7 million/cmm. and she was readmitted to the ward, but without any treatment the count rose spontaneously to 4.0 million in 2 wk. and she was returned to outpatient status for observation. Four months later symptoms began to recur and she re-entered the hospital at the age of 10½ yr. The physical examination was unchanged except for a diminution of vibratory sense

in the toes. Glossitis was not marked. RBC count was 1.1 million/cmm., Hgb. 7 gm./100 cc., WBC count 3.8 thousand/cmm. with 56% lymphocytes. No reticulocytes were present. Gastric analysis revealed no free hydrochloric acid after histamine. The marrow showed megaloblastic hyperplasia.

She was given vitamin B_{12} 5 μg. by mouth each morning at 6 a.m. During the first week of this treatment the reticulocytes remained below 1%. She was then given 150 cc. of normal gastric juice each morning with the B_{12}. On the third day of this treatment subjective improvement was noted followed by an increase of reticulocytes to 16% on the 7th day, at which time the RBC count was 1.8 million/cmm. The patient was then given 30 u. of liver extract intramuscularly weekly, which brought about a rapid restoration of the RBC count to 3.7 million/cmm. at the end of the next fortnight. At this time neurologic examination was normal. Up to the time of this report she has been maintained in satisfactory remission with bimonthly injections of liver extract.

Summary (See chart 1): C. Z. had 11 relapses of a profound anemia between the ages of 2 and 10 yr. At the age of 9 yr., 6 mo., the anemia was noted to be macrocytic and the marrow megalo-

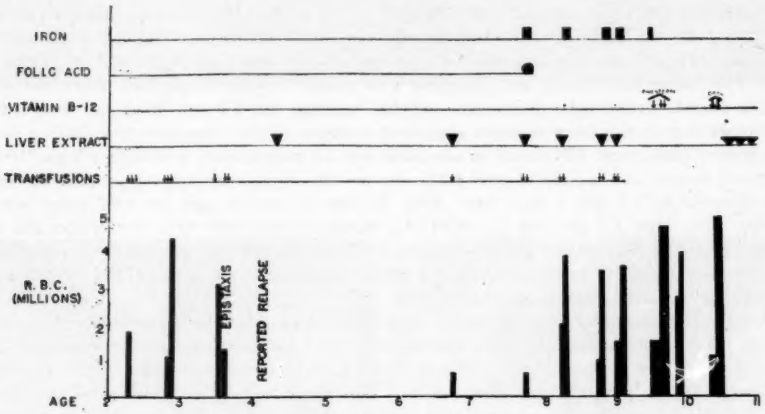

CHART 1. Juvenile pernicious anemia in Patient C. Z. Sequence of relapses and remissions during 9 yr.

blastic. Vitamin B_{12} was given parenterally with optimal response. The blood was allowed to relapse again and vitamin B_{12} was found to be ineffective by mouth, unless accompanied by normal gastric juice. Other features of note were the absence of any demonstrable other cause for the anemia; recurrent atrophic glossitis responding to therapy; minimal neurologic changes in the lower extremities, and spontaneous remission. On 2 separate occasions achlorhydria was noted during relapse, but free hydrochloric acid was subsequently found after remission had been effected. The patient is being satisfactorily maintained on parenteral liver therapy.

Case 2. (Figs. 1 and 3.) V. Z., the younger sibling of the previously described patient, was first seen at Bellevue Hospital at the age of 8 yr. for a nonspecific vaginitis. At this time she was slightly anemic with RBC count 4.0 million/cmm. and Hgb. 11 gm./100 cc. for which she was treated with iron. During the next 3 mo. she developed easy fatigability, anorexia, exertional dyspnea, pallor and a painful tongue, and she re-entered the hospital. She appeared well developed and nourished but pale, with a lemon yellow tint to the skin. The tongue was smooth, shiny and red with atrophy of the papillae on the tip and margins (Fig. 1B). The liver edge was palpable 2 cm. below the costal margin. Neurologic status was normal. RBC count 1.7 million/cmm. with Hgb. 6.1 gm./100 cc.; WBC 7.0 thousand/cmm. with 50% lymphocytes; reticulocytes 2.8%; MCV 130 cμ. Aspirated marrow contained 60% megaloblasts. Gastric contents were hypochlorhydric. Gastrointestinal RGs were normal. Stool examinations revealed no ova or parasites and normal fat content. The patient was given ferrous sulfate 1.2 gm. daily for 10 days. Within 2 wk., the RBC count had fallen to 1.3 million/cmm. No reticulocytes were demonstrable. The next day, vitamin B_{12} 10 μg. were given intramuscularly. There was a prompt subjective improvement and relief of glossitis within 4 days, and

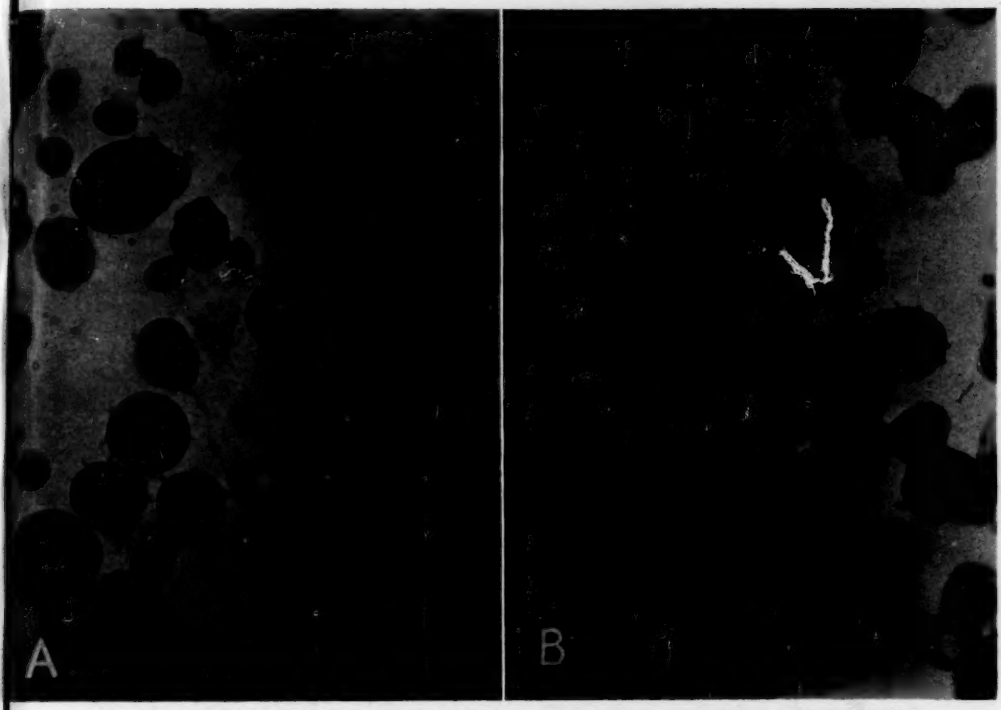

FIG. 3. Patient V. Z. A. Marrow before treatment. B. Marrow 3 wk. after treatement with vitamin B_{12}.

reticulocytosis of 13.8 and 16.4% was reported on the fourth and eighth day after therapy. After 2 wk. the RBC count was 3.2 million/cmm. and the Hgb. 10.0 gm./100 cc. At this time the marrow showed normoblastic hyperplasia.

The patient was allowed to relapse for further study, and was readmitted 6 mo. later with pallor but no distress. She was an aggressive, active child without glossitis. The physical examination was essentially normal except for hypoactive deep reflexes in the lower extremities. Position and vibratory senses were normal. RBC count 2.8 million/cmm. with Hgb. 9.0 gm./100 cc., WBC 7.4 thousand/cmm. with 52% lymphocytes and 3 megaloblasts/100 WBC. Reticulocytes were 0.6%. The marrow was megaloblastic. Gastric analysis revealed hypochlorhydria before histamine (free HCl 7; total 24).

Five micrograms of vitamin B_{12} were given orally each day at 6 a.m. and continued for 1 wk. During this time reticulocytes did not rise above 1%. A repeat gastric analysis showed no free HCl and 10 μ. of total acid before histamine. After 0.25 cc. of a 1/1000 solution of histamine phosphate subcutaneously, there were 9 u. of free HCl and 27 u. of total acid in the gastric secretion. For the next 9 days the same dose of histamine subcutaneously was given together with oral vitamin B_{12} 5 μg. Again no reticulocyte response was observed. At the end of this time the RBC count had fallen to 2.3 million/cmm. The 5 μg. of oral B_{12} were then accompanied each day with 150 cc. of normal gastric juice. There was a prompt reticulocyte response reaching a peak of 10% on the 7th day of this therapy. RBC count rose to 3.2 million/cmm. and Hgb. 12.5 gm./100 cc. 11 days later. The marrow was now normoblastic. The patient has since been followed in the clinic with bimonthly injections of liver extract, on which she has kept well up to the present time (see chart 2).

Summary: V. Z. is the 8 yr. old sibling of C. Z. She likewise had a macrocytic, megaloblastic anemia with glossitis, relieved by parenteral vitamin B_{12} therapy. Her gastric juice contained small amounts of free hydrochloric acid, which could be increased by histamine injection. Histamine, how-

ever, did not appear to stimulate the secretion of intrinsic factor. Oral vitamin B_{12} was ineffective unless normal gastric juice was given with it.

Case 3. J. M. was a male infant whose grandfathers were first cousins. When he was 4 mo. old his mother noticed that his tongue was beefy red and appeared to be sore, a condition that recurred throughout the first year despite attempted treatment for "thrush." At the age of 1 yr., a persistent diarrhea with occasional vomiting developed, lasting for 2 mo. Starvation for the diarrhea aggravated the tongue condition. Three months later an acute tonsillitis occurred for which he was treated with a sulfonamide drug for 3 days. Following this he had intermittent fever, anorexia and weight loss of 2.3 kg. and his mother noticed an increasing yellowish hue of the skin.

At the age of 1 yr., 5 mo., he was noted to be pale and somewhat icteric and was found to be severely anemic. Hgb. 6.6 gm./100 cc., RBC count 2.6 million/cmm. There was 2+ albuminuria with occasional granular casts in the urine. Following a blood transfusion and parenteral crude liver

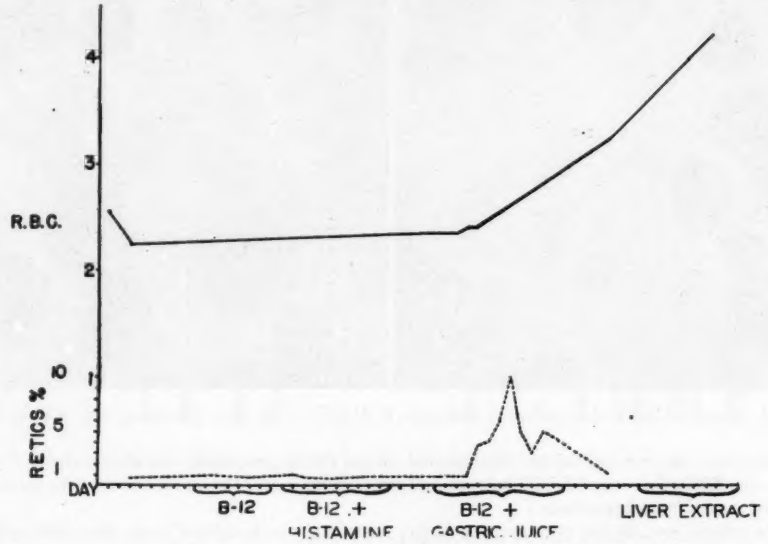

CHART 2. Patient V. Z. Effect on red blood cell levels and reticulocytes of oral vitamin B_{12} with and without normal gastric juice.

extract he showed 9.8% reticulocytes, and despite an intervening attack of croup RBC count rose to 4.3 million/cmm.

A month later he had another upper respiratory infection which was followed by diarrhea and sore tongue, persisting for 5 wk., and the RBC count fell to 3.8 million/cmm. with Hgb. 10.8 gm./100 cc. Albuminuria and casts were again noted. The tuberculin test was positive but 3 yr. later a tuberculin patch test was negative. He was given iron ammonium citrate (containing approximately 16% iron), 4 cc. thrice daily, and 3 injections of 1 cc. of crude liver extract. After 6 wk. the RBC count was slightly over 4.0 million/cmm.

For the next year he grew and developed normally, although he was noted to be less active physically than most children his age. At the age of 3 yr., 2 mo., he became increasingly drowsy and pale, refused meals, lost weight and developed puffiness of the face. Physical examination showed pallor and yellowish skin, as well as a liver palpable 3 cm. below the costal margin, sluggish knee jerks, absent ankle jerks and bilateral Babinski signs. Hgb. 5.7 gm./100 cc., RBC count 1.2 million/cmm., WBC count 10.6 thousand/cmm., 50,000 platelets and 2 nucleated RBC/100 WBC. The red cells were macrocytic. The icteric index was 27.3. He was given a blood transfusion, a variety of oral vitamin preparations, and crude (2 u.) and refined (10 u.) liver extract daily on alternate days. Five days after beginning liver extract, reticulocytosis of 12% was noted and the Hgb. and

RBC count had risen to 9.9 gm./100 cc. and 3.0 million/cmm., respectively. He was now more alert but his gait was ataxic and he stumbled and fell easily. Speech was slow and inarticulate. A gastric analysis 9 days after the start of liver therapy revealed free hydrochloric acid. Liver therapy was reduced to 1 cc. of the crude product daily. On this therapy gait and speech improved but the diminished knee and absent ankle jerks and Babinski signs persisted. Sternal marrow examined after 3 wk. of liver treatment was normal. Psychometric examination showed an I. Q. of 59. Following adenoidectomy he was maintained on oral iron therapy and 1 tablespoon thrice daily of ventriculin®.* At this time his RBC was 4.7 million/cmm.

Six months later, his speech and gait were described as normal and he could run. Knee and ankle jerks were present and equal. The Babinski signs were still present. RBC count was 4.3 million/cmm. with Hgb. 11.1 gm./100 cc. He received ventriculin® intermittently. Seven months later there was no clinical disease present but the RBC count had fallen to 3.5 million/cmm. Two months later because of "anemia," oral folic acid 10 mg. daily was started.

Because of recurrent upper respiratory infections his tonsils were removed 5 mo. later, at which time neurologic examination revealed active and equal superficial and deep tendon reflexes and no Babinski signs. Coördination and sensory modalities were described as normal. Hgb. was 13 gm./100 cc. and the RBC count 4.5 million/cmm. Two weeks after operation, he walked with difficulty and talked poorly. Oral folic acid 10 mg. was continued daily but his symptoms grew progressively worse until he was admitted for the first time to Babies Hospital at the age of 5 yr., 1 mo.†

Physical examination revealed a well developed and well nourished 5 yr. old with a blank facial expression, who kept his mouth open and his tongue between his teeth. There was some gingivitis but no glossitis. Speech was labored and he was slow in his mental responses. His legs were weak and his gait unsteady. The muscle bundles of the extremities, particularly the legs, were poorly defined and flabby. Deep reflexes in the arms were active and equal, but markedly diminished in the knees and absent in the ankles. Plantar stimulation showed extension of the big toe bilaterally, with fanning of the other toes on the left only. Sensory examinations were unsatisfactory due to the patient's inability to cooperate.

Hgb. 11.0 gm./100 cc., RBC count 2.8 million/cmm. and WBC 7.3 thousand/cmm. with 55% neutrophiles and 40% lymphocytes. The mean cell volume was 144 cμ. Reticulocytes were 0.6%. The bone marrow exhibited megaloblastic hyperplasia. The gastric contents contained normal amounts of free hydrochloric acid. The spinal fluid was normal. The urine showed 1 to 3+ albuminuria but was negative for phenylpyruvic acid and porphyrin. Serum bilirubin was 1.57 mg./100 cc. Determinations of alkaline phosphatase, cholesterol, serum proteins, cephalin flocculation, glucose tolerance, vitamin A tolerance and sedimentation rate were all normal. Mantoux and Kline tests were negative. The duodenal juice contained normal trypsin and slightly reduced amylase. The stool fat and starch content were normal. A roentgenographic skeletal survey showed normal maturation. Intravenous pyelography was normal. An electroencephalogram showed a diffusely abnormal record with a high content of medium voltage 4 to 6/sec. activity.

During the 1st 17 days in the hospital the patient became increasingly lethargic, talked and ate less, could not stand, and became incontinent of urine and feces, and a convulsion lasting 60 sec. was observed. On the 18th day, folic acid 10 mg. daily by mouth was resumed. In the next 8 days there was a marked acceleration of the down hill course. At the end of this time he was extremely lethargic, sleeping over 20 hr. a day, inarticulate and completely incontinent. Knee and ankle jerks were absent and Babinski signs present bilaterally. He did not move his lower extremities at all. During this time there was no hematologic improvement and the reticulocyte counts remained under 1%.

In this critical condition, folic acid was stopped and 3 cc. of intramuscular crude liver extract was administered daily. Twelve hours after the second dose the patient sat up in bed, asked for toys and ate a large meal without urging. For the first time in 10 days he responded to questions. The dose of liver extract was increased to 5 cc. (10 U.S.P. u.) daily and continued for 5 wk. Reticulocytosis

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* Ventriculin® (Parke-Davis)—oral preparation of desiccated hog stomach. 1 tablespoon equals ¼ U. S. P. antianemic u.

† All previous hospitalizations were at the New York Infirmary for Women and Children. The authors are indebted to the administration of that institution for making available the data contained in this report.

up to 9% was observed on the 7th day of treatment. In the next few weeks there was a marked improvement in the condition of his gums, and in the amount and quality of his speech. He started to move his legs in bed but complained of pains in them. Fecal and urinary incontinence persisted. The lower limb tendon reflexes remained absent and the Babinski signs persisted. The bone marrow had returned to a normal appearance at the time of discharge (2 mo. after admission) and the blood contained Hgb. 12.5 gm./100 cc. and RBC count 4.0 million/cmm.

After 2 wk. of 60 cc. daily of Valentine's oral crude liver extract (45 cc. equals 1 U.S.P. u.), he was able to bear weight on his legs without support. By 3 mo. he could walk quite well by himself and incontinence had ceased. Very sluggish knee jerks could be obtained. The dose of oral liver extract was reduced to 30 cc. daily. A month later the knee jerks were active and equal and shortly afterwards the ankle jerks had also returned to normal. Babinski signs remained present, and he walked with a slapping gait. There was some weakness of the anterior tibial muscles, most marked on the left. The vibratory and position senses were not measurable due to inability to cooperate. The gait, appearance and behavior suggested that of a patient with cerebral palsy.

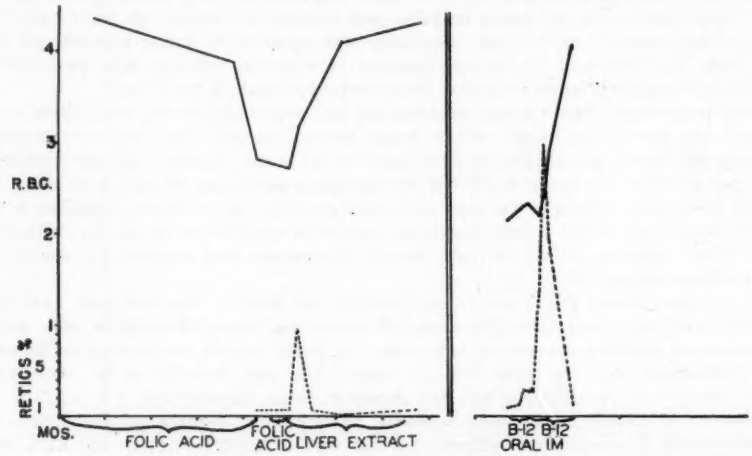

CHART 3. Red blood counts and reticulocytes in J. M., showing failure to respond to folic acid and oral vitamin B_{12}, and prompt response to liver extract and intramuscular B_{12}.

All medication was stopped 7 mo. after discharge and his condition remained unchanged for 6 mo., when an RBC count of 3.5 million/cmm. was noted. Shortly afterward his appetite became poor and he began to stumble and drag his left leg. The next month the marrow showed slight megaloblastic change, and a gastric analysis showed 20 u. of free and 48 u. total acidity in the fasting specimen. The tongue was reddened around the edges. He continued to show intermittently poor appetite and red tongue for the next 7 mo.

A month later, at the age of 7 yr., 1 mo., Hgb. was 9.0 gm./100 cc., RBC count 2.1 million/100 cc., WBC count 4.9 thousand/100 cc., 69,000 platelets and 1% reticulocytes. The peripheral blood smear showed 23% neutrophiles, of which many were hypersegmented, 72% lymphocytes and 1 nucleated RBC/100 WBC. There was marked anisocytosis and poikilocytosis, polychromasia and macrocytosis. The marrow showed megaloblastic hyperplasia with 73% megaloblasts and many giant metamyelocytes.

For 7 days he was given vitamin B_{12} 15 μg. daily by mouth, with a maximal reticulocyte count of 3% on the fourth day. The same dose of vitamin B_{12} was then given daily intramuscularly, with a rise in the reticulocytes to 30% after 6 days. The dose was then reduced to 15 μg intramuscularly every 2 to 3 wk. Two weeks after intramuscular therapy was started Hgb. was 12 gm./100 cc., RBC count 4.0 million/cmm., and WBC 7.3 thousand/cmm. with 64% neutrophiles, platelets 264,000 and reticulocytes 1.3%. The tongue appeared normal and appetite and activity were markedly improved.

The patient has been maintained up to the present on vitamin B_{12} 15 μg. every 2 to 3 wk., paren-

terally. He has remained well except for the persistent abnormal neurologic pattern. When the patient was 7 yr., 7 mo. old, RBC count was 5.8 million/cmm. Three months later gastric analysis showed histamine refractory achlorhydria. Psychometric examination at this time reported "low end of borderline intelligence for his age."

Summary: (See chart 3): Between the ages of 15 mo. and 7 yr., this boy had 4 episodes of profound macrocytic anemia with megaloblastic bone marrow. Three responded to parenteral and oral liver extract therapy, and the fourth to parenteral, but not oral, vitamin B_{12}. Sore tongue was an inconstant accompaniment of relapse. At 3 yr. neurologic abnormalities were noted. Folic acid maintained the blood for a while, but the nerve involvement was unimproved. Subsequently, folic acid markedly aggravated the neurologic condition and failed to influence the anemia which had relapsed. The response to liver extract was in marked contrast. Repeated gastric analyses disclosed free hydrochloric acid until the age of 7 yr., 10 mo., when histamine refractory achlorhydria was demonstrated. The patient is being satisfactorily maintained on vitamin B_{12}, but there is evidence of permanent damage to the central nervous system.

Case 4. B. M., the brother of J. M., was first seen at the age of 22 mo. because of known anemia in the sibling. He had had poor appetite and increasing pallor ever since an upper respiratory infection at the age of 17 mo. At 20 mo. the family doctor reported the Hgb. to be 40 gm./100 cc., and the patient was given 6 tablespoons of Valentine's oral liver extract daily for a period of 17 days with resulting improvement. Physical examination revealed a well developed, well nourished, active infant, with no abnormalities except a liver palpable 3 cm. below the costal margin. Neurologic examination was normal. Hgb. was 11.8 gm./100 cc. and 6 wk. later with no further medication, it had risen to 13 gm./100 cc.

Nine months later pallor again became evident. He had received 3 tablespoons of liver extract for several days, approximately 1 wk. before he was seen. At this time Hgb. was 12.5 gm./100 cc.; RBC count 2.8 million/cmm.; WBC 8.1 thousand/cmm. with 32% neutrophiles, 6% eosinophiles and 60% lymphocytes. There were 0.8% reticulocytes. The smear showed adequate numbers of platelets, moderate anisocytosis, slight poikilocytosis, rare stippled red cells and a number of hypersegmented polymorphonuclear neutrophiles.

When seen 3 wk. later the patient appeared well. The physical examination was negative except for moderate reddening of the tongue. Hgb. was 13.5 gm./100 cc. and RBC count 3.1 million/cmm.

During the next few months the patient had a 2 day febrile episode of unknown cause and a bout of pneumonia. He began to complain of leg pains and his mother stated that he was unable to run, and that, although previously able to walk up and down steps, he now waited for her to help him. Walking was now slow and unsteady. He had little energy and slept a great deal. His intelligence was said to be average. He had been given Valentine's liver extract 32 gm. orally at the time of the pneumonia, which had produced some improvement, but not in his ability to walk.

Examination revealed a sleepy 3 yr. old child, with no pallor or icterus. The gait was slightly ataxic but there was no stumbling. Muscle tone was normal. The knee jerks were exaggerated, the ankle jerks were normal. The Babinski sign was equivocally present on the left side only. There was no Romberg sign. Vibration, touch and position sense could not be evaluated. Hgb. was 12.0 gm./100 cc.; RBC count 4.0 million/cmm., WBC 7.2 thousand/cmm., platelets 184,000, reticulocytes 0.3%. The blood smear showed some macrocytosis and a few hypersegmented polymorphonuclear neutrophiles. The urine contained 2+ albumin. The marrow was hyperplastic with early megaloblastic changes. Giant metamyelocytes were seen.

After 2 wk. his appetite was still poor and his gait unchanged, but an increase in activity had been noted. He walked with a slapping gait on a broad base, with marked lumbar lordosis. The knee jerks were now hyperactive, the ankle jerks absent, and Babinski, Oppenheim and Chaddock signs were present on both sides. The RBC count had fallen to 3.8 million/cmm. and 2 mo. later was 3.5 million/cmm.

At 3½ yr. the RBC count was 2.8 million/cmm. with Hgb. 12.5 gm./100 cc. and reticulocytes 1.2%. Because the patient's brother had responded to vitamin B_{12}, this drug was given intramuscularly, in 15 μg. doses every other day, for 3 wk. Reticulocytosis of 7.3% was observed on the 7th day of vitamin B_{12} therapy and the RBC count was 4.5 million/cmm. 4 wk. after its start. Subsequently vitamin B_{12} was given, 15 μg. intramuscularly, every 3 wk.

The patient has been seen at periodic intervals up to the present. Hgb. has ranged between 13.7 and 15 gm./100 cc. and his RBC count between 5.0 and 6.2 million/cmm. He has remained well

and there has been a marked improvement in motor ability, which was first noted approximately 3 wk. after the start of vitamin B_{12}. After 3 mo. he was able to run and to ride a small bicycle. However, at 3 yr., 10 mo. of age, there had been no change in the neurologic examination, and the knee jerks were still hyperactive, the ankle jerks absent, and the Babinski signs equivocal bilaterally. Four months later gastric analysis showed histamine refractory achlorhydria. Psychometric examination 1 mo. later showed "high-grade defective intelligence."

Summary: B. M. is a sibling of J. M., previously described. Although his early course was obscured by the frequent administration of crude liver extract by his mother, a macrocytic, megaloblastic anemia was demonstrated at the age of 3½ yr. At approximately 3 yr. of age, he had begun to show difficulty in walking. Following intramuscular vitamin B_{12} therapy, the blood count was restored to normal, and motor activity and gait were markedly improved, although abnormal neurologic signs persisted. Gastric analysis, 8 mo. after the beginning of vitamin B_{12} therapy, revealed histamine refractory achlorhydria.

Discussion

These four patients between them present all the features commonly associated with adult pernicious anemia with the exception of persistent histamine refractory achlorhydria and premature greying of the hair.

Hematologic Findings: In each case the anemia was usually macrocytic with a high color index and increased mean corpuscular volume. In the few instances when this was not the case it will be noted that the patient was in the toddler period of life, when iron deficiency is common. In every case, by the time the syndrome was well established the macrocytic character of the anemia was apparent. The blood smears showed marked anisocytosis and poikilocytosis with many large oval macrocytes, and at times basophilic stippling and circulating megaloblasts were encountered. Leukopenia was a concomitant feature with neutropenia. Macropolycytes with as many as eight lobes were occasionally seen. The platelet counts were low or normal. Reticulocytes were markedly reduced in absolute number.

The appearance of the marrows was identical with that of pernicious anemia in comparable stages of relapse. When the patients were severely anemic, promegaloblasts and basophilic megaloblasts predominated in the red cells series and myeloid-erythroid ratios were characteristically reduced or even inverted. Giant metamylocytes were present.

Following specific therapy with liver extract or vitamin B_{12}, there was a change in the character of the marrow to a normoblastic type of hematopoiesis. This was reflected in the peripheral blood by increasing reticulocytosis, rise in red cells and hemoglobin, and leukocytosis due to an increase of neutrophiles. The size and shape of the red cells returned to normal.

In the three cases in which it was determined, the serum bilirubin was found to be elevated due to an increase in the indirectly acting component.

Absence of Other Causes for the Megaloblastic Anemia: In none of these children was there any evidence of sprue, celiac disease, fish tapeworm infestation, or other abnormalities of the gastrointestinal tract, as indicated by history, roentgenogram or study of the stool for ova and fat. The diets of all were apparently adequate and there was no evidence of any associated vitamin deficiency. In the case of the Z family, two siblings on the same diet were well. That the condition was not analogous to megaloblastic anemia of infancy was indicated by the fact that it relapsed repeatedly after treatment, and responded to vitamin B_{12} in all cases, and not to folic acid in the case of J. M. There was nothing to suggest hypothyroidism in these children and where a basal metabolism test could be done, in the two older children, it was normal. Liver function was normal

as indicated by most of the tests done. In the case of C. Z. some hepatic dysfunction when she was in relapse was indicated by elevated thymol turbidity and bromsulfonphthalein retention tests, but both of these tests were normal when repeated after the blood count was restored. In short, by a process of elimination one would have arrived at a diagnosis of pernicious anemia even if it had not been possible to demonstrate the absence of intrinsic factor in the gastric juice.

Familial Incidence: In the Z family there was no history of anemia in the parents, and two older siblings were examined and found to be normal. The two patients bore a striking physical resemblance to each other. In the M family the parents (who were second cousins) were not anemic and there were no other siblings. These two patients also showed a marked physical resemblance to each other.

Kaufmann and Thiessen[21] reported multiple occurrence of pernicious anemia in 8 out of 48 families. Stamos[22] found a familial incidence of 7.9% of 645 cases. Many other observers have noted a familial tendency to the disease. It is striking that among the cases listed in table 1 consanguinity and/or pernicious anemia (or probable pernicious anemia) occurred in 8 of the 14 families represented.

Remissions and Relapses: In the preliver days relapse and remission were characteristics of pernicious anemia that were relied on heavily in making the diagnosis. The explanation for spontaneous remission in the disease must be that either because of a greater intake of vitamin B_{12} or folic acid in the diet, or a transient increase of intrinsic factor, or alterations in the intestinal bacterial flora, enough antianemic substance is absorbed to effect remission. C. Z. exhibited a relapse to less than 3,000,000 red cells followed by a spontaneous return of the blood to levels over 4,000,000 in a few weeks. A persistent relapse did not occur until five months later.

Pernicious anemia patients also exhibit marked variation in individual requirements for antianemic substance, and the time before relapse following cessation of therapy ranges from months to years.[23] B. M.'s requirements in this respect were apparently lower than the other children's, since his blood exhibited a definite responsiveness to the administration of small amounts of oral liver extract. His brother maintained a normal blood count for 18 months without therapy and C. Z. received no treatment between the ages of 4 and 6½ years.

In connection with the discussion of remissions it should be noted that transfused blood may contain sufficient quantities of antianemic substances to bring about reticulocytosis and induce normoblastic maturation in a megaloblastic marrow. The long history of failure to diagnose the case of C. Z., even in hospitals where the marrow was examined, was partly due to this fact. It may take as long as several weeks for a marrow to return to a megaloblastic appearance following transfusion of a pernicious anemia patient. All patients with anemias profound enough to require transfusion and for whom marrow studies are contemplated should have them done prior to the administration of blood.

It is perhaps significant that many of these patients' relapses were preceded by episodes of acute infection. It is well known that concomitant infection may impair the response to specific therapy in pernicious anemia,[24] and it has also been shown that occasionally vitamin C deficiency may have the same effect.[25] Moreover, May[26] has shown that vitamin C deficiency plays an important role in the pathogenesis of the folic acid deficient state characteristic of megaloblastic anemia of infancy. Whether or not infections, which exhaust vitamin C levels,[27] might have made the patients more prone to vitamin B_{12} deficiency is purely speculative.

Glossitis: One of the commonest features of pernicious anemia is atrophy of the mucosal surface of the tongue. In some cases this is accompanied by a markedly inflamed and painful glossitis. This is not a constant feature in every relapse, but is frequently a sign of impending relapse. After repeated episodes of glossitis, permanent papillary atrophy may result. Both of the Z's and J. M. exhibited glossitis which responded promptly and rapidly to specific treatment. In none of the patients was it a constant finding with every relapse, but it twice heralded a hematologic relapse in the case of C. Z.

Neurologic Findings: In the preliver days the incidence of serious involvement of the central nervous system in pernicious anemia was apparently great, and in some reports as high as 95% of patients[28] were said to show evidence of such disease. It is difficult to be certain that minor degrees of impaired vibratory perception in the toes of elderly patients are on a specific basis, however, and significant evidence of combined system disease is now found in about a fifth of pernicious anemia patients.[29] It is possible that some patients may be constitutionally more susceptible to nervous system involvement. The condition is most frequently found in the dorsal columns and pyramidal tracts, but peripheral nerve degeneration and involvement of the cerebral cortex with diffuse demyelination have also been shown to occur.[30] It is important to distinguish cerebral symptoms due to anemia which clear following transfusion, from those that represent specific lesions. While the motor tracts often respond well to specific therapy, degeneration of the dorsal columns of any duration is much less reversible, and patients with combined system disease usually show a persistent impairment of vibratory sense and slapping gait.

Repeated experiences have shown that while vitamin B_{12} and folic acid can both effect hematologic improvement, only the former will help the neurologic lesions.[31] In most instances folic acid has no effect on coexisting cord disease and in some instances the neurologic disturbance is aggravated, sometimes with fulminating rapidity.[32] The explanation for this is not clear, but apparently while both substances are required for blood maturation, only B_{12} influences the nervous tissue metabolism. The relationship between folic acid and vitamin B_{12} is gradually becoming more apparent. Shive's studies [33, 34] have indicated that both substances participate in enzymatic fashion in the synthesis of such varied substances as thymidine, serine, choline and hypoxanthine from their respective precursors, reactions that involve the transfer of a single carbon atom. Welch[35] has shown that folic acid aids the synthesis of methyl groups. One may postulate that both are required for the maturation of blood cells, and in conditions where one is absent, the other will be relatively ineffective. This hypothesis explains the failure of pernicious anemia of pregnancy and megaloblastic anemia of infancy to respond to B_{12} on the grounds that they are primarily folic acid deficiencies. On the other hand, pernicious anemia is primarily a B_{12} deficiency and responds best to that agent. Vilter[36] has observed that such patients, maintained on folic acid for years, required progressively larger amounts of folic acid to maintain their blood and finally ceased to respond to it altogether, but responded promptly when vitamin B_{12} was administered. This phenomenon was observed in J. M. In chicks put on a folic acid deficient diet, signs of the folic acid deficiency develop more rapidly if vitamin B_{12} is given concurrently[37] and liver extract does not prevent the development of folic acid deficiency in swine on a folic acid deficient diet.[38] Possibly the two substances are in equilibrium with each other in the body and administration of one hastens the disappearance of the other, under certain conditions. This seems a logical hypothesis to explain the aggravation of central nervous system lesions in patients with pernicious anemia receiving folic acid.

Of the patients described in this study, C. Z. showed only transient minor neurologic changes during relapse which cleared promptly when treatment was instituted, and her sister showed none. Both M's, on the other hand, showed severe neurologic disturbance from an early age. In the case of J. M., anemia antedated the appearance of central nervous system involvement by 18 months, and in the younger child by about a year. Both children exhibited pyramidal tract involvement and ataxic gait, and the older child also had evidence of diffuse central nervous system involvement during his severe relapse. Both patients showed prompt improvement with liver extract orally or parenterally, and parenteral B_{12}, but J. M.'s condition was markedly and rapidly aggravated by folic acid. Both patients have evidence of residual neurologic damage.

Gastric Analyses: Three of the four patients had free hydrochloric acid in the gastric contents after histamine, and in many instances it was present without such secretory stimulation. In the case of C. Z. it was noted on two separate occasions that there was no free acid in the fasting specimen when the patient was in relapse but that it reappeared when she was in remission. The M's both showed histamine refractory achyorhydria, but J. M. did not develop it until 6½ years after he was first found to be anemic. This suggests the possibility that a process in the gastric mucosa similar to the glossitis accompanied relapse, and that repetition of such episodes might lead to the atrophic gastritis picture commonly associated with pernicious anemia. If such were the case the atrophy of the gastric mucosa and achlorhydria would be the result rather than the cause of lack of intrinsic factor. It will be important to follow these patients to see if over the years they develop or continue to show persistent achlorhydria while being maintained throughout on adequate antianemic therapy.

Demonstration of Absence of Intrinsic Factor: For many years hematologists have accepted the view of Castle[39] that extrinsic factor in the food reacted with intrinsic factor in the stomach secretions to form a third substance, the antipernicious anemia principle, which was stored in the liver, whence it was released to act upon the maturation of cells in the bone marrow. We now know that the substance in liver that cures pernicious anemia is vitamin B_{12}, and that it is also present in foods and can be extracted from beef muscle.[40] Berk et al.[41] have shown that B_{12} behaves like extrinsic factor in that it requires the presence of intrinsic factor to be absorbed from the gastrointestinal tract, and Hall[42] demonstrated that the substance in gastric juice that promoted the absorption of B_{12} was heat labile. Like extrinsic factor, B_{12} alone will produce a remission if fed in large enough amounts,[43] but in doses of 5 μg. it is ineffective unless accompanied by intrinsic factor supplied as 100 to 150 cc. of normal gastric juice or equivalent preparations.[44] This gives us an indirect method of testing for the presence of intrinsic factor, since, if the patient can be shown to respond to parenteral B_{12} but fails to respond to B_{12} given orally, there must be some defect in absorption. If this defect is corrected by the simultaneous administration of normal gastric juice it is logical to assume that it was due to a lack of intrinsic factor in the patient's own gastric juice.

This presumptive test can be checked if desired by collecting gastric juice from the patient and feeding it for a week or 10 days, together with extrinsic factor, to a patient with known pernicious anemia in relapse. The amounts of gastric juice necessary for such a test are too large to collect easily from a patient with achylia gastrica, so the Reimann test[20] was devised. It is based on the observation that the incubation of suboptimal doses of liver (20 gm.) with small amounts of gastric juice (20 cc.) resulted in a 20 to 30 fold potentiation of the antianemic effect of the liver. The Reimann technic, if positive,

is evidence of the presence of intrinsic factor. Since the amounts of liver and gastric juice used in the test are so small that some subjects' gastric juice and some portions of liver, containing less than their full quotas of intrinsic and extrinsic factor, respectively, may give negative results, a negative test is not conclusive evidence of the absence of intrinsic factor.

In the case of these children, all were shown to respond to parenteral vitamin B_{12} and three were shown not to respond to it when given orally. Both Z's responded promptly to oral vitamin B_{12} accompanied by normal gastric juice. A Reimann test done with C. Z.'s gastric juice gave negative results. Stimulation of gastric secretion by histamine concomitantly with oral B_{12} did not enhance intrinsic factor secretion in V. Z. Both of the M. children now have histamine refractory achlorhydria. From this evidence it appears indisputable that the cause of the anemia in these four children is a lack of absorption of vitamin B_{12}, due to absent intrinsic factor in the gastric juice.

Summary

Histories have been presented of two pairs of sibling children with recurrent macrocytic anemia with megaloblastic bone marrow responding specifically to liver extract and vitamin B_{12}.

The clinical features and laboratory findings were similar to those of adult pernicious anemia in every respect except for the inconstant presence of histamine refractory achlorhydria. All the patients responded to vitamin B_{12} given parenterally, but in three to whom it was given by mouth no response was obtained. Two of these subsequently responded to oral B_{12} when it was accompanied by normal gastric juice. The other two developed histamine refractory achlorhydria while in hematologic remission. This is interpreted as proof that the anemia was due to deficient intrinsic factor in the gastric juice.

Three patients showed evidence of disease of the spinal cord, in two of whom the symptoms were severe. These symptoms were compatible with a diagnosis of dorsolateral sclerosis, and improved with antipernicious anemia therapy. In one of these patients, treated with folic acid, the neurologic lesions were aggravated severely.

Pernicious anemia due to the absence of gastric juice intrinsic factor occurs in children. The presence of free hydrochloric acid in the gastric contents does not preclude the possibility of the disease.

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SPANISH ABSTRACT

Anemia Perniciosa Infantil

La ocurrencia de anemia perniciosa debida a la ausencia del factor intrinsico de Castle en el jugo gastrico, es extremadamente rara en niños. Una revisión extensa de la literatura médica mundial solamente reveló doce casos probados de anemia perniciosa en niños, a los cuales el presente reporte añade cuatro nuevos casos. Estos últimos ocurrieron en dos pares de hermanos de 7-9 y 3-7 años de edad respectivamente, todos los pacientes presentaron una anemia macrocitica con médula ósea megaloblastica, la cual respondió especificamente al extracto de higado y a la vitamina B_{12}, pero recurrió invariablemente con la suspension temporaria del tratamiento. La ocurrencia de aclorhidria gastrica después de la histamina, no fué un sintoma constante, pero sin embargo estuvo presente en todos los casos a intervalos variables. La anemia de un paciente respondió favorablemente a la inyección parenteral de vitamina B_{12}, pero no se obtuvo mejoría cuando ésta fué admistrada por via oral. En dos pacientes pudo demonstrarse que la administración oral de vitamin B_{12} fué ineficaz en la ausencia de jugo gastrico normal. Basandose en esta observación, los autores concluyen que la mera presencia de acido clorhidrico no significa la presencia del factor intrinsico de Castle, y por lo tanto no elimina el diagnóstico de anemia perniciosa. Dos pacientes presentaron signos neurologicos severos de degeneracion medular, y un tercer paciente exibió alteraciones neurologicas ligeras durante las recurrencias de la anemia. En un paciente las lesiones neurologicas fueron intensificadas con la administración de acido fólico. La occurrencia de glositis fué un sintoma inconstante durante las recurrencias hematologicas de la anemia. En todos los casos la administración de un tratamiento anti-anemico adecuado a intervalos regulares, resultó en la cesación de las recurrencias y en el mantenimiento satisfactorio de la remisión hematologica.

401 West 118 Street

RELATIVE EFFECTIVENESS OF VITAMINS A AND D IN OIL AND IN WATER

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THE original observations of Clifford[1] stimulated several investigators[2-10] to study the various factors influencing the absorption of vitamin A, such as the vehicle in which it is dissolved, its chemical form and the particle size. The rapidity of absorption has been measured by the level of vitamin A in blood after test doses. Various investigators have reported that higher blood levels are found after the administration of aqueous, than after oily solutions of the vitamin, particularly in premature infants, and in children with impaired intestinal function.

Since the blood levels do not measure retention or utilization, and since it is not feasible to determine the liver storage of vitamin A in infants, Lewis[2] and Sobel[3] determined the liver storage of vitamin A in rats after administering aqueous and oily solutions of the vitamin. The findings were confirmatory of the blood levels, i.e., greater storage occurred with the aqueous than with the oily preparations. In explanation, Lewis[2,4] reported that infants excreted by way of the gastrointestinal tract large percentages of vitamin A when it was administered in oily form.

In all these studies, large doses of vitamin A were employed. In man, dosages of 1,500 to 17,000 units/kg. were administered;[2,4-10] and in the rat the dosage range was 9,600 to 95,000 units/kg.[2-4] Such large doses were necessary because of the limited sensitivity of the method available to determine vitamin A in blood and in tissues.

Vitamin A deficiency results in cessation of growth, xerophthalmia, keratinization of tissues and night blindness. In order to know the relative effectiveness of different preparations of vitamin A, it is necessary to determine their effectiveness in the prevention or cure of these symptoms. Neither rapid absorption nor liver storage is definitive in regard to vitamin A therapeusis.

The object of this study was to determine whether there is any difference in the effectiveness of fat-soluble vitamins in aqueous and oily vehicles, for the cure of vitamin A and vitamin D deficiencies. In order to accomplish this purpose, minimal doses of vitamins in the range of the therapeutic requirement were administered.

EXPERIMENTAL

Vitamin A

Observations on Growth: Series I.—Effect of Daily Doses at Different Levels

Rats of the inbred Wisconsin strain, weighing between 40 and 50 gm. and not exceeding 28 days of age, were placed on a vitamin A-deficient ration* until symptoms characteristic of vitamin A deficiency developed. During the period of depletion the rats were

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* The ration consisted of casein 18, salt mixture 4, yeast 5, dextrinized starch 62.5, cottonseed oil 8, purified cellulose (Ruffex) 2.5 and vitamin D 75 units %.

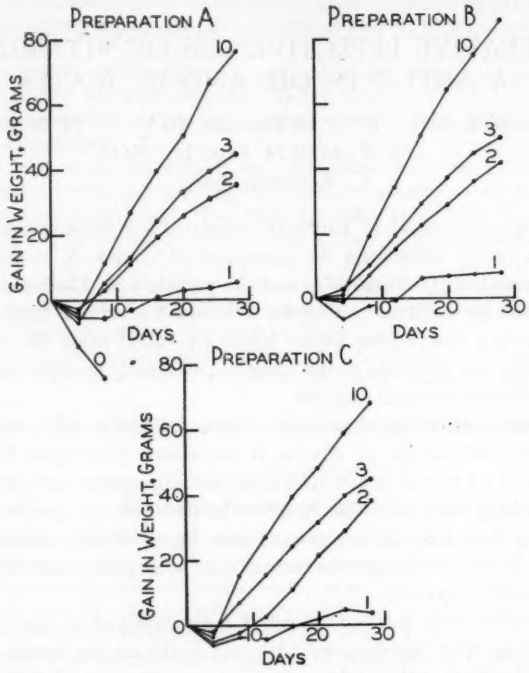

CHART 1. Weight response of vitamin A-depleted rats given for 28 days low daily doses of vitamin A in aqueous (A), emulsion (B) or oily (C) form. Numeral on each curve indicates in units daily dose of vitamin A per rat.

weighed every four days and when vitamin A deficiency became manifest the eye condition was evaluated as (1) normal, (2) watery and light-sensitive, (3) swollen with bloody exudate or (4) purulent with opacity of the cornea.

Thirteen groups of A-depleted rats, each consisting of 12 rats distributed as to sex and litter, were placed on the experiment. Each group was fed daily by syringe, 1, 2, 3 or 10 U.S.P. units of vitamin A. Three vitamin A preparations were employed. Preparation A* was miscible with water and contained vitamin A palmitate in a vehicle of glycerine, water, polyoxyethylene sorbitan monooleate and propylene glycol. Preparation B† was a dry powder containing the natural distilled esters of vitamin A in small droplet form, protected against oxidative loss by a thin film of carbohydrate and acacia. It was free from synthetic solubilizers. When added to water it gave an opalescent emulsion. Preparation C‡ contained vitamin A as it occurs naturally in fish liver oils.

* Known under the trade name of Mead's Poly-Vi-Sol. It contains, in addition to the vehicles itemized above, irradiated ergosterol, ascorbic acid, thiamine hydrochloride, riboflavin, niacinamide and small amounts of inert ingredients.

† Known under the trade name of Mead's Polyvitamin Dispersion. It contains all the vitamins itemized in the preceding footnote, and is a dry powder, consisting principally of dextrose and lactose. Small amounts of acacia, cottonseed oil and concentrated vegetable tocopherols are present in the powder.

‡ Known under the trade name of Mead's Oleum Percomorphum. Consists of liver oils of percomorph fishes, viosterol® and other fish liver oils. The vitamin A is presumably present in the natural ester form. The preparation is an oil immiscible with water.

The three preparations will be referred to as the aqueous, emulsion and oily forms of vitamin A. A single lot of each of the three preparations was used for the entire study and was assayed for vitamin A content by the official spectrophotometric method.[11] Dilutions of each preparation were freshly made each day from an assayed stock supply. The concentration of each was adjusted so that each rat would receive a volume of 0.2 cc./day. Preparations A and B were diluted with water and Preparation C was diluted with cottonseed oil. The negative control group received 0.2 cc. of cottonseed oil/day. The rats of all groups were offered the vitamin A-free diet *ad libitum* during the assay period.

Results.—The average weight responses of the 13 groups of 12 rats each are given in chart 1. The increase in weight during the assay period is plotted against the number of days during which the specific dosage of vitamin A was administered. The aqueous, emulsion and oily forms are plotted separately to show the effect on growth of increasing levels of vitamin A. The rapid failure in growth of the control group is given on the chart for Preparation A. Inspection shows that the weight increments with comparable levels of vitamin A were identical for the three preparations; for example, two units of vitamin A

TABLE 1

GAIN IN WEIGHT (GM.) AT END OF 28 DAY FEEDING PERIOD FOLLOWING ADMINISTRATION OF 3 DIFFERENT VITAMIN A PREPARATIONS

Dosage Level	Aqueous	Emulsion	Oily
1 unit	5.4	8.0	3.6
2 units	35.3	41.2	38.3
3 "	44.5	49.2	44.5
10 "	75.9	85.1	67.7

in the aqueous, emulsion and oily media gave weight gains of 35.3, 41.2 and 38.3 gm., respectively. Net gains in weight for the four dosage levels at the end of the 28 day period are shown in table 1.

There was no statistical difference between the weight responses in any of the groups at a given unitage level. The t value for the maximum weight difference was 1.6—and was less than required for significance. From the shape of the curves and the magnitude of the weight responses, it would appear that vitamin A in aqueous, emulsion and oily forms is equally effective in promoting the growth of vitamin A-deficient rats.

The eye condition (xerophthalmia) was given a numerical value at the time the animals were placed on test and subsequently at the end of the 28 day assay period. The degree of improvement in the eye condition was similar for all preparations at comparable dosage levels, irrespective of the vehicle. Complete cure of xerophthalmia was observed at the 10 unit dosage level, and the improvement in the eyes paralleled closely the magnitude of the weight response.

Observations on Growth: Series II.—Effect of Single Small Doses

Even though the aqueous solutions of vitamin A are more readily absorbed and give greater liver storage, or less fecal excretion when administered at high dosage, these factors may not be effective so far as growth is concerned when minimal doses of 1 to 10 units are fed daily. In order to further study the operation of these factors, single doses

of vitamin A were administered to vitamin A-deficient rats. By varying the number of units in the administered dose, and by giving single doses, there was an opportunity for rapid absorption, increased liver storage or decreased fecal excretion to be manifest by the improved performance of the animals. For example, if there were larger liver storage after administration of the water-soluble form of the vitamin, the vitamin A-deficient animal should survive for a longer period than when given an equal dose of the oily form.

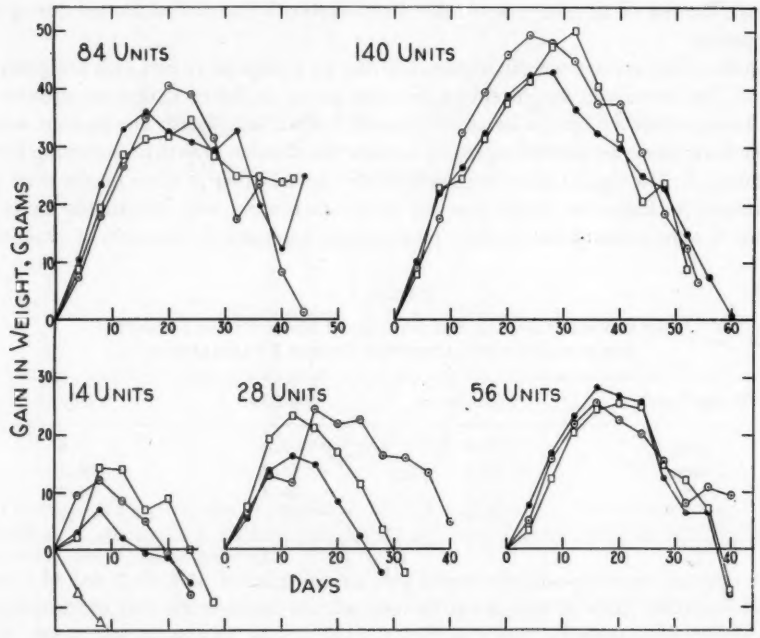

CHART 2. Weight response of vitamin A-depleted rats to single doses of vitamin A administered in aqueous, emulsion or oily form. Legend: Aqueous ●——●, emulsion ⊙——⊙, oil □——□.

Similarly, if one preparation should cause more or less fecal loss of the administered vitamin A, the net effect should be observed in weight gain or survival.

Rats* were depleted of vitamin A as previously described and groups of 10, distributed as to sex and litter, were given single doses of 14, 28, 56, 84 or 140 U.S.P. units of vitamin A. Preparations A, B and C were employed, and were of the same lots as previously described. The dose was administered by stomach tube in a total volume of 0.4 cc. Preparations A and B were diluted with a suitable amount of water and Preparation C with cottonseed oil. The control group received 0.4 cc. of cottonseed oil. Changes in weight were followed by weighing the rats on every second day, and the eye condition and its subsequent change were evaluated on the basis previously described.

Results.—The growth responses are given in chart 2. The control rats receiving no supplement continued to lose weight and died within 3 to 24 days. At the 14-unit level,

* Rats of the Sherman strain from Rockland Farms, New City, N.Y.

the maximum gain in weight was 14 gm. for the oily preparation and 7 gm. for the aqueous preparation. The variation in weight at this low dosage level does not have statistical significance. At dosage levels of 56 units, 84 units and 140 units, the growth curves are almost superimposed, and indicate the equivalence of vitamin A in the three preparations. Minor fluctuations in the curves are attributed to the death of rats in the group. There is no difference in the average survival time of rats in any of the groups, suggesting that there is no significant difference in liver storage, and, conversely, incon-

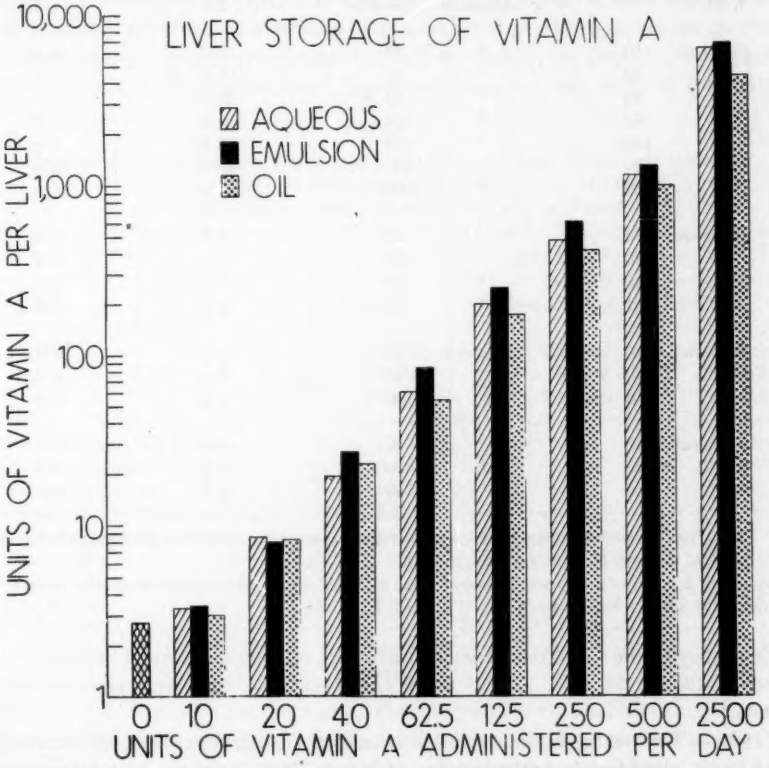

CHART 3. Liver storage of vitamin A by A-depleted rats fed graded doses of vitamin A in aqueous, emulsion or oily form. Units stored are plotted on logarithmic scale.

sequential differences in fecal loss. If there was more rapid absorption in the case of one preparation than of another, it had no ultimate effect on the growth or survival of the vitamin A-deficient rats.

Liver Storage: Series III.

To measure liver storage, higher dosages of Preparations A, B and C were given. The procedure was to give vitamin A-deficient rats a daily dose of vitamin A in the form of one of the three described preparations. Five daily doses were administered by stomach tube, and 48 hours after the last dose the animals were killed, the livers removed, and individually assayed for vitamin A content. The method of extraction of the livers prior

TABLE 2

SIGNIFICANCE OF DIFFERENCES IN AVERAGE VITAMIN A CONTENT OF RAT LIVERS AFTER ADMINISTRATION OF VARIOUS LEVELS OF VITAMIN A IN DIFFERENT MEDIA

Preparation		Compared With		Differences Between Means, u. of Vitamin A	"t" Values*
Control		Aqueous	(10 u.)	0.6	1.2
Aqueous	10	"	20	5.2	8.3
"	20	"	40	10.7	6.9
"	40	"	62.5	40.9	17.7
"	62.5	"	125	136.0	42.8
"	125	"	250	271.0	37.0
"	250	"	500	640.0	40.0
"	500	"	2500	4970.0	56.0
Aqueous	10	Oil	10	0.3	0.6
"	20	"	20	0.3	0.2
"	40	"	40	2.6	1.1
"	62.5	"	62.5	6.3	2.9
Aqueous	10	Emulsion	10	0.1	0.2
"	20	"	20	0.6	0.6
"	40	"	40	7.5	3.8
Emulsion	10	Oil	10	0.4	0.7
"	20	"	20	0.3	0.2
"	40	"	40	4.9	2.1

* The "t" values were calculated according to Fisher (Statistical Methods for Research Workers, ed. 5, London, Oliver & Boyd, Ltd., 1934, p. 120).

Values of 2.1, with 18 degrees of freedom have a P=.05; "t" values of 2.88 or greater have a P of less than 0.01 and are highly significant (Fisher, p. 158).

to their assay by the Carr-Price antimony trichloride reaction was devised by Ames et al.[12] Doses of 10, 20, 40, 62.5, 125, 250, 500 and 2,500 units daily were given to each of 10 rats.

Results.—The average values, expressed as units of vitamin A per liver, are presented as a bar graph, plotted on logarithmic paper in chart 3. The columns are arranged to show in sequence the effect of administering the aqueous, emulsion and oily forms. Table 2 gives the t values for differences in storage between the three forms. When no vitamin A was given there was an observed value of 2.7 units of vitamin A per liver. At a dosage level of 10 units, the vitamin A storage in the liver was only 3.3 units—not significantly different from the control. When the dosage level was increased to 20 units daily for the five day period, there was a significant increase in liver storage, but no significant difference in storage between the three preparations. At 40 units daily there is a further significant increase in liver storage, but there is no difference in the storage on the aqueous and oily forms. There was greater storage when the emulsion was fed than when either the aqueous or the oily form was given, and this difference is statistically significant. This is evident at each dosage level above 20 units daily.

Table 2 emphasizes the large increase in liver storage as the dosage level of the aqueous

preparation is increased. Similar increments in storage, each highly significant, were observed with the oily and emulsion forms. Both table 2 and chart 3 show that at low levels of intake there is identical liver storage with the aqueous and oily forms, but that at high levels, e.g., 62.5 units daily there is more storage with the aqueous preparation. This is confirmatory of earlier work at high dosage levels.

A dosage level of 20 units daily is approximately four times the amount necessary to cure vitamin A deficiency in the rat (160 units/kg. body weight). The level considered adequate for prevention of vitamin A deficiency in a variety of animals and in man is 25 to 35 units/kg.[13] Thus, at low dosage levels and even at a level approximately 4 to 7 times that necessary to prevent vitamin A deficiency, there is no detectable difference in the liver storage of the vitamin from aqueous, emulsion and oily forms of the vitamin.

TABLE 3

AVERAGE HEALING RESPONSES OF RICKETIC RATS GIVEN EQUAL AMOUNTS OF VITAMIN D SUPPLIED AS OLEUM PERCOMORPHUM, CALCIFEROL AND ACTIVATED 7-DEHYDROCHOLESTEROL DISSOLVED IN OIL AND IN WATER

Substance Assayed	ASSAY					
	No. 1		No. 2		No. 3	
	No. Rats	Average Healing Response	No. Rats	Average Healing Response	No. Rats	Average Healing Response
Oleum Percomorphum in Oil	9	1.97+	7	1.89+	11	2.09+
Oleum Percomorphum in Water	10	2.15+	11	2.13+	10	2.15+
Calciferol (D_2) in Oil	8	1.93+	8	1.64+	9	1.78+
Calciferol (D_2) in Water	8	1.55+	7	1.93+	9	1.56+
Activated 7-Dehydrocholesterol (D_3) in Oil	10	1.68+	14	1.95+	11	2.05+
Activated 7-Dehydrocholesterol (D_3) in Water	11	1.89+	13	1.88+	5	1.40+

Vitamin D

Therapy of Rickets.—Factors influencing the absorption of fat-soluble vitamin A should similarly influence the absorption of fat-soluble vitamin D. To determine whether the vehicle would have any effect on the antiricketic effectiveness of the different vitamins D, the following experiments were undertaken: Rickets was induced in weanling rats according to the procedure outlined in the U.S. Pharmacopoeia, XIII. Three substances were tested for antiricketic action—vitamin D_2 (califerol), vitamin D_3 (activated 7-dehydrocholesterol) and a fish liver oil preparation (oleum percomorphum) containing both natural D and calciferol. All three preparations were administered in oil and in aqueous solution to rats (table 3). Cottonseed oil was the diluent for the calciferol, activated 7-dehydrocholesterol, and the fish liver oil. The aqueous solutions were made by using polyoxyethylene sorbitan monooleate (Tween 80) in appropriate amounts.

Each ricketic rat was given sufficient solution (oily or aqueous) to supply 0.0125 μg. daily of the active agent. The amount of fish liver oil given in either of the two vehicles was 45.4 μg.—calculated as equivalent to 0.0125 μg. of vitamin D.

Results.—The healing response was measured by the line test at the end of the standard

7 day assay period. The average healing is given in table 3. Three assays of each preparation were conducted using the indicated number of rats for each assay. Statistical comparison of the degree of healing showed clearly that identical amounts of vitamin D presented to the rat in oily or aqueous media result in identical healing responses. It seems clear that the vehicle in which vitamin D is dissolved exerts no detectable influence on the healing response of ricketic rats.

Discussion

The blood level of vitamin A after a large oral dose is closely related to the vehicle in which the vitamin is dissolved—aqueous solutions and emulsions give higher blood levels than do oily solutions. Liver storage of the vitamin is likewise proportionately larger. The dosages employed by various investigators to demonstrate differences in liver storage were in the order of 5,000 units of vitamin A/kg. body weight because of the limited sensitivity of the chemical or spectrophotometric method used to determine vitamin A. The level required to prevent vitamin A deficiency is regarded as about 25 units/kg., or only 1/200th of a dose of 5,000 units.

To measure the relative effectiveness of vitamin A in different vehicles, it is necessary to have comparative studies in which the test dosages are given at physiologic levels. High blood levels or greater liver storage are significant only if they can be correlated with more efficient therapeusis or prophylaxis of vitamin A deficiency.

On administration of very low doses (1, 2, 3 or 10 units daily) of vitamin A in aqueous, emulsion and oily media to vitamin A-deficient rats, there was an immediate response in growth and improvement of xerophthalmia. Vitamin A carried by the three preparations was quantitatively equivalent in its effect on the deficiency. However, since the dosage was low, and given daily, the effect of rapid assimilation (as claimed for the aqueous or emulsion form) may have been masked. For this reason, single small doses of the vitamin in different vehicles were given to vitamin A-deficient rats. They were then continued on the vitamin A-deficient diet and their growth response and length of survival compared. As shown in chart 2, the rats receiving the vitamin in the three forms behaved similarly during their entire life after the single dose, indicating that rapid absorption *per se* is without significance in the therapy of vitamin A deficiency.

Liver storage of the vitamin was studied by giving 10, 20, 40, 62.5, 125, 250, 500 or 2500 units daily for 5 days to vitamin A-deficient animals. These doses are lower than most of those used by others[2-4] and were graded in order to find the level at which storage could be demonstrated, and to determine if there is a change in storage of the three preparations as the dose is increased. At the 20-unit level the three preparations caused identical amounts of vitamin storage and at the 40-unit level the aqueous and oily forms resulted in equivalent storage. These findings are different from those of Lewis[2,4] and Sobel[3] but their experimental conditions, particularly in regard to dosage and period of administration, were correspondingly different. Lewis gave rats single doses of 13,000 units, which is a much larger amount on a weight basis than would ever be administered to an infant.

Lewis observed that at high dosage levels the particle size was important in attaining high blood levels and large liver storage. The three preparations employed by the present investigators had approximately the same particle sizes as those that Lewis employed; i.e., submicroscopic, 0.3 to 6.5 μ and macroscopic for the aqueous, emulsion and oily solutions, respectively. At low dosage levels the authors have observed none of the marked

differences that Lewis and others have reported. Since these levels are of the magnitude necessary for the prevention and cure of vitamin A and D deficiency, the authors cannot believe that particle size *per se* is important for the assimilation of fat-soluble vitamins at therapeutic levels.

Since the vitamin D is fat-soluble, and subject to the same factors that influence the absorption of vitamin A, observations were made to determine whether, at critical and minimal dosage levels, any difference in the antiricketic effectiveness of the three vitamin D preparations in oil or in water could be demonstrated. The answer was in the negative. All preparations were equally effective in inducing healing of the ricketic process.

Vitamin A deficiency is not common in premature infants,[6] in those with pancreatic insufficiency,[14] or in the population at large. This favorable event is due to the recognition of the importance of vitamin A in nutrition, to its general recommendation by physicians, and to the well-balanced diet that is available to most people. The oily forms of vitamin A, as cod liver oil and various fish liver oil concentrates, are widely used and are probably responsible to a large extent for the absence of vitamin A deficiency. The availability of water-soluble forms of the vitamin simplifies the problem of administration of vitamins A and D, facilitates rapid absorption when this is important, and avoids the fishy taste of liver oils. But, therapeutically, in vitamin A deficiency, the oily and water-soluble forms must be regarded as equivalent.

Conclusions

When small doses of vitamin A (1, 2, 3 or 10 units) in water solution, emulsion or oil solution were fed to vitamin A-deficient rats, their gain in weight and the improvement of xerophthalmia were equal at comparable dosage levels.

When single doses (14, 28, 56, 84 or 140 units) of the same three vitamin solutions were given to vitamin A-deficient rats, there was again no difference in the average gain in weight or survival of comparable groups.

The liver storages of vitamin A after feeding graded amounts of the vitamin to vitamin A-deficient rats were equal for the water and oil solutions at comparable dosage levels of 10, 20 and 40 units. At higher dosages the water solution resulted in larger storage than the oil solution.

The antiricketic effectiveness of calciferol, activated 7-dehydrocholesterol, and a mixture of vitamin D as in fish liver oil was the same irrespective of whether the vitamin was supplied in water or in oil.

The data are interpreted to mean that the rapid absorption, or greater liver storage, that results from large doses of water solutions of vitamin A is of no consequence at dosage levels required to quantitate therapeutic effect.

Acknowledgment

The authors wish to express appreciation to Robert L. Henry, James G. Hilakos, Wilbur H. Martin, Vernon C. Bender and Leroy W. Frick, without whose technical assistance these studies would have been impossible.

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SPANISH ABSTRACT

La Eficacia Relativa de Vitaminas A y D en Forma Oleosa y Acuosa

Cuando dósis pequeñas (1, 2, 3 y 10 unidades diarias) de vitamina A en forma acuosa, en emulsión y en preparaciones oleosas, fueron administradas a ratas deficientes en vitamina A, la repuesta obtenida sobre el crecimiento y en la curación de la xeroftalmia, fué similar con todas las formas de suspension empleadas a dosis comparables. La administración de una sola dósis relativamente pequeña (14 a 140 unidades) de vitamina A, no causó diferencias evidentes sobre el aumento de peso, ni en la sobrevivencia de las ratas de grupos comparables.

Cuando dósis pequeñas de vitamina A (10, 20, 40 unidades) fueron administradas a ratas deficientes, los depósitos en el higado fueron iguales con el uso de ambas preparaciones (acuosa y en aceite). La administración de dósis mas altas de vitamina A en forma acuosa y en emulsion, resultó en un aumento de los depósitos de vitamina en el higado, mucho mayores que los obtenidos con el uso de mezclas en aceite.

La eficacia antiraquitica del calciferol, 7-dehidrocolesterol y de mezclas de vitamina D en aceite de higado de pescado, fué similar en las ratas, independientemente del vehiculo empleado (agua o aceite).

En conclusión, los autores señalan, que la rapida absorción y deposición en el higado, observados durante la administración de dósis excesivas de ciertas preparaciones de vitamina A, no son caracteristicos de la eficacia terapeutica cuando estas preparaciones son usadas a dosis profilacticas ordinarias. Con estas dosis ordinarias los autores demonstraron una eficacia similar, tanto con las preparaciones en aceite, como con las emulsiones ó suspensiones acuosas.

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MODIFICATION OF THE TECHNIC OF TREATING ERYTHROBLASTOSIS FETALIS BY EXCHANGE TRANSFUSION

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THE purpose of exchange transfusion in erythroblastosis fetalis is to disrupt the combination of Rh agglutinogen and Rh antibody that is present in the body of the erythroblastotic infant. Since it is not feasible to remove the Rh antibodies, the baby's coated red blood cells are removed and replaced by other cells (Rh-negative) which are not affected by these antibodies. The idea that Rh antibodies produce their effects by direct action on the tissue cells seems doubtful in view of the observation that exchange transfusion arrests the progress of the disease, even when substantial amounts of antibody remain in the infant's body at the completion of the procedure and for several weeks or months thereafter. Although there is a correlation between the degree of anemia at birth and the severity of the disease in the infant during the neonatal period, hemolysis is not the cause of the neurologic sequelae as shown by the observation that such sequelae occur with equal frequency regardless of the severity of the initial anemia. Wiener[1,2] has suggested that the antibodies produce their effects not merely by hemolysis but also by producing intravascular conglutination, thus blocking the circulation to vital organs. Exchange transfusion is the most efficient method of combatting the anemia, and if carried out promptly after birth also forestalls the occurrence of intravascular conglutination.

When performing an exchange transfusion, it was found convenient at first to withdraw and inject 500 cc. of whole citrated blood, a quantity twice as great as the average baby's blood volume. Whether the procedure is carried out continuously, or intermittently with the aid of syringes, an exchange transfusion with twice the baby's blood volume will replace approximately 86.5% of the baby's blood.[3] By increasing the amount of blood used in the exchange to 1,000 cc., the efficiency of the procedure can be increased to 98.2%.[4] However, such a procedure is rather strenuous for a severely affected infant, and subjects the baby to the introduction of large quantities of citrate and adult plasma, the latter being objectionable because of its conglutinating properties.[5] Other workers[6] have therefore suggested a modification of the procedure in which 50 cc. of the baby's blood is withdrawn before starting the exchange.* This is then replaced before the procedure is terminated. In this way the efficiency of an exchange transfusion of 500 cc. can be increased from 86 to more than 90%. Moreover, as Wasserman and Sharney[7] have emphasized, it is the percentage of red cells replaced which is important, and those infants with the most pronounced anemia are the ones in whom the percentage replacement of red cells is the highest.

The purpose of the present paper is to present a further modification of the procedure

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*While at first the authors hesitated to adopt the procedure through fear of producing shock, they found upon trial that the babies withstood this withdrawal of blood very well.

TABLE 1

FINAL HEMATOCRIT AND PERCENTAGE OF INAGGLUTINABLE CELLS AFTER EXCHANGE TRANSFUSION WITH PACKED RED CELLS OF HEMATOCRIT 0.75

Volume of blood transfused (cc.)	Per cent replacement*	Hematocrit of donor's cells in baby's circulation at end of transfusion	Baby's initial hematocrit 0.50		Baby's initial hematocrit 0.40		Baby's initial hematocrit 0.30		Baby's initial hematocrit 0.20		Baby's initial hematocrit 0.10	
			Final total hematocrit (per cent)	Per cent inagglutinable cells	Final total hematocrit (per cent)	Per cent inagglutinable cells	Final total hematocrit (per cent)	Per cent inagglutinable cells	Final total hematocrit (per cent)	Per cent inagglutinable cells	Final total hematocrit (per cent)	Per cent inagglutinable cells
0	0	0	50	0	40	0	30	0	20	0	10	0
10	3.92	2.94	50.98	5.77	41.31	7.12	31.76	9.26	22.16	13.27	12.55	23.43
20	7.69	5.77	51.92	11.11	42.69	13.04	33.46	16.65	24.23	22.99	15.00	37.14
30	11.31	8.48	52.82	16.05	43.96	19.29	35.09	24.16	26.22	32.34	17.55	48.88
40	14.79	11.09	53.75	20.63	45.17	24.50	36.65	30.26	28.13	39.42	19.61	55.27
50	18.13	13.60	54.53	24.94	46.35	29.34	38.16	35.64	29.97	45.38	21.79	62.40
60	21.34	16.00	55.33	28.91	47.46	33.71	39.59	40.42	31.73	50.43	23.87	67.03
70	24.42	18.32	56.11	32.58	48.55	37.73	40.99	44.69	33.44	54.78	25.88	70.76
80	27.39	20.54	56.84	36.24	49.60	41.45	42.34	48.45	35.08	58.61	27.82	73.90
90	30.23	22.67	57.56	39.39	50.57	44.83	43.60	51.99	36.72	61.74	29.75	76.20
100	32.97	24.73	58.29	42.43	51.54	47.87	44.84	55.15	38.13	64.86	31.43	78.68
110	35.60	26.70	58.90	45.33	52.46	50.92	46.02	58.02	39.68	67.29	33.14	80.57
120	38.12	28.59	59.53	48.03	53.34	53.60	47.15	60.64	40.97	69.78	34.78	82.19
130	40.55	30.41	60.14	50.56	54.19	56.12	48.25	63.03	42.30	71.89	36.36	83.64
140	42.88	32.16	60.75	52.96	55.01	58.46	49.30	65.28	43.58	73.80	37.87	84.92
150	45.12	33.84	61.33	55.18	55.79	60.65	50.30	67.27	44.82	75.50	39.33	86.04
250	63.21	47.41	65.80	57.23	62.12	76.32	58.45	83.00	54.77	86.56	51.09	92.80
500	86.47	64.85	71.62	90.55	70.26	92.30	68.94	94.06	67.66	95.85	66.20	97.96

* On assumption that baby's blood volume is 250 cc.

of exchange transfusion which was designed to shorten and simplify the operation, and eliminate certain dangers inherent in the original.

In the operation to be described packed red cells are introduced into the baby's body, instead of whole citrated blood, at the same time that blood is withdrawn. This has the advantage that relatively insignificant quantities of citrate and adult plasma are introduced and, in addition, because of the shorter time in which the operation can be carried out, only minimal quantities of heparin are required. The almost complete elimination of citrate also obviates the necessity for the administration of calcium, which in the whole citrated blood procedure was nearly always required to counteract the tetanogenic effect of the citrate. The avoidance of the introduction of large amounts of adult plasma is an important advantage because adult plasma contains large amounts of conglutinin which, in in vitro tests, causes clumping of red cells coated with univalent antibodies. Infants' plasma, on the other hand, is relatively deficient in producing conglutination.[5] The procedure is terminated when 120 to 150 cc. of packed cells have been injected and an equal quantity of blood has been withdrawn, the volume depending on the severity of the anemia. In contrast to exchange transfusion with 500 cc. to 1,000 cc. of whole blood, which require a minimum of 60 to 90 minutes, the modified procedure takes only 25 to 30 minutes.

Mathematic Considerations

As was demonstrated in a previous paper,[3] the percentage replacement of whole blood resulting after exchange transfusion is given by the formula, $100(1 - \frac{1}{e^v})$, where v represents the amount of blood used in the procedure expressed as a fraction of the infant's blood volume. In table 1 (second column) the numerical value of the percentage replacement for a baby with a blood volume of 250 cc. has been calculated and tabulated. Appropriate corrections can easily be made for babies whose blood volumes are more or less than 250 cc. For example, for a baby with a blood volume of 200 cc., 100 cc. of blood would have the same effect as 125 cc. of blood for a baby with a blood volume of 250 cc. ($v = 0.5$), so that the degree of replacement would lie between 38.12 and 40.55%. Since this represents the replacement of whole blood, the percentage replacement of red cells in specific instances must be calculated by taking into account the hematocrits of the patient's and the donor's bloods.

The blood used by the authors in the exchange transfusion is freshly drawn into citrate solution, and then distributed among sterile 50 cc. "potato" tubes. The cotton plugs are fastened down with rubber bands and the blood centrifuged at 1500 rpm for 15 minutes, and the supernatant plasma removed as completely as possible with the aid of a 50 cc. syringe and a long aspirating needle. The sedimented cells are pooled and used for the transfusion. Blood prepared in this manner has a hematocrit of approximately 0.75.* Therefore by multiplying the figures in the second column of table 1 by 0.75 (h_d), one obtains the hematocrit of the donor's blood in the patient's circulation at the end of the transfusion. To determine the infant's total hematocrit at the termination of the transfusion, one must add to this the hematocrit of the baby's own red cells still remaining in his circulation. The latter depends upon the baby's initial hematocrit and

* This will vary within narrow limits depending on the degree of packing of the cells, and the thoroughness with which the supernatant plasma is aspirated. Too tight packing is to be avoided so that the cells are not damaged and the blood remains fluid enough to be injected.

the amount of blood exchanged, and is derived by multiplying the amount of the baby's whole blood still remaining (e^{-v}) by its hematocrit (h_p). That is, one has merely to deduct the figure in column 2 from 100% and multiply this by the baby's initial hematocrit. The resulting value added to the figure in the third column gives the final hematocrit. In brief, the final hematocrit equals $h_d(1 - e^{-v}) + h_p e^{-v}$.* To determine the percentage of inagglutinable cells present at the end of the transfusion, which is usually considered the index of efficiency of the procedure, the hematocrit of the donor's cells is divided by the final hematocrit. These results have been calculated and tabulated for babies with different hematocrits in the appropriate columns of table 1.

While the object of the procedure is to achieve the highest percentage of inagglutinable cells possible, an important limiting factor is the hematocrit of the baby's blood at the end of the procedure. Theoretically, if the procedure is continued long enough the baby's hematocrit would approximate that of the donor's packed blood and the baby's blood would become so viscous that it could not circulate. It was felt that a hematocrit of about 62% was a safe upper limit to set. In the cases treated, therefore, the procedure was terminated after 150 cc. of packed cells had been administered in the case of infants with low hemoglobins, while in babies with normal hemoglobins as little as 100 cc. of packed cells were used. While this policy resulted in a satisfactory exchange in anemic babies, in babies whose hemoglobins were initially high the percentage of inagglutinable cells at the end of the procedure would be only about 50%. There is, however, a correlation between the severity of the illness and the degree of anemia, and apparently this percentage of replacement is adequate for the milder cases.

The accuracy of the figures in table 1 were checked in a number of cases by performing blood counts, hematocrits and differential agglutination studies before and after the transfusion. For example, in one instance before the transfusion the Hgb. was 14.6 gm./100 cc., RBC count 4.92 million/cmm. and the hematocrit 0.56. After the exchange transfusion the hemoglobin concentration was 18.9 gm./100 cc., RBC count 6.28 million/cmm. and the hematocrit 0.62. The differential agglutination tests showed that approximately half the cells were Rh-positive at the end of the procedure, as was expected.

In the original procedure, using whole citrated blood, it was the custom to transfuse 50 to 100 cc. more blood than was withdrawn. The reason for this was that the blood used had been diluted with citrate solution which would subsequently be eliminated from the baby's circulation. This margin was also necessary to insure that the baby's blood count would be close to normal so that subsequent transfusion would not be necessary. In the simplified procedure described here the same volume is transfused as is withdrawn, and this has the advantage of minimizing circulatory strain.

The treatment of erythroblastosis can be classified into four categories: (1) multiple simple transfusions of whole citrated blood, (2) multiple transfusions of packed red cells, (3) exchange transfusion with whole citrated blood and (4) exchange transfusion with packed red cells. When the outcome is successful, this depends upon the replacement of the baby's cells by other red cells not agglutinable by the maternal antibodies, the difference being that in simple transfusion therapy the baby's cells are eliminated by hemolysis instead of being actually withdrawn from the body. The difference between the four methods of treatment is represented diagrammatically in chart 1.

* A similar formula was published by Veall and Mollison[8] for intermittent exchange transfusion after this paper was submitted for publication.

COMPARISON OF FOUR DIFFERENT METHODS OF TREATING TYPICAL ERYTHROBLASTOSIS FETALIS BY TRANSFUSION OF Rh-NEGATIVE BLOOD

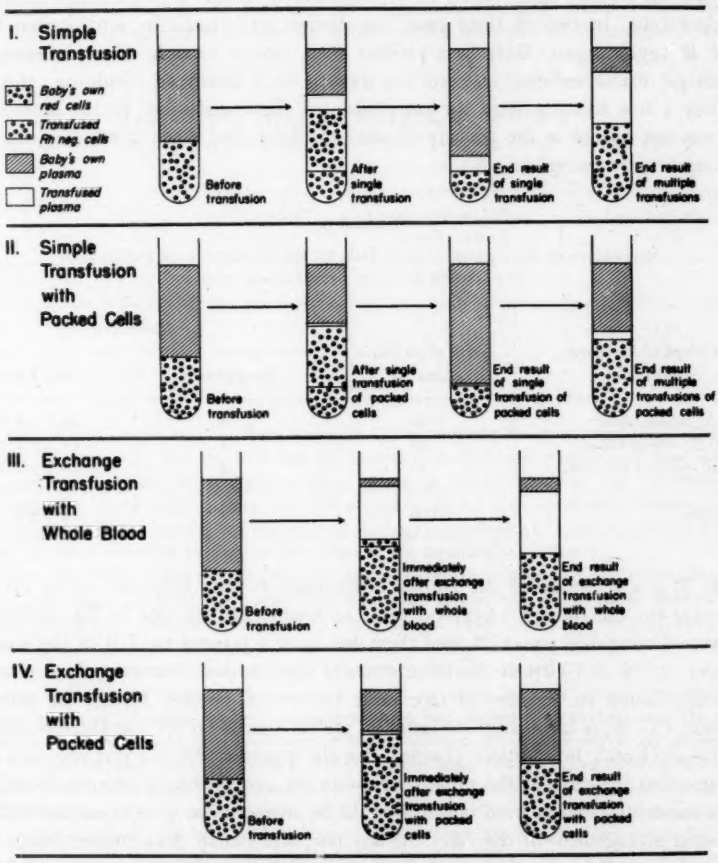
I. Simple Transfusion
Baby's own red cells
Transfused Rh neg. cells
Baby's own plasma
Transfused plasma
Before transfusion
After single transfusion
End result of single transfusion
End result of multiple transfusions
II. Simple Transfusion with Packed Cells
Before transfusion
After single transfusion of packed cells
End result of single transfusion of packed cells
End result of multiple transfusions of packed cells
III. Exchange Transfusion with Whole Blood
Before transfusion
Immediately after exchange transfusion with whole blood
End result of exchange transfusion with whole blood
IV. Exchange Transfusion with Packed Cells
Before transfusion
Immediately after exchange transfusion with packed cells
End result of exchange transfusion with packed cells

CHART 1. Comparison of 4 Different Methods of Treating Typical Erythroblastosis Fetalis by Transfusion of Rh-negative Blood.

Concerning the choice of donors for exchange transfusion in erythroblastosis fetalis, it is clear on the basis of patients that have been successfully treated with simple transfusions of whole maternal blood[9] that the antibodies do not produce their harmful effects by direct action on tissue cells. The mother then is an ideal donor for the simplified exchange transfusion with packed cells and, in fact, the authors recently had occasion to resort to the use of maternal blood for this purpose. The mother's red blood cells are always compatible, not only in erythroblastotis due to Rh sensitization, but also in cases due to Hr, A-B and other blood factors, as well as in multiple sensitization.[10] While the small

amount of maternal serum trapped in packed cells would be harmless to the baby whose cells are already coated, if desired, the mother's red cell could be washed once or twice with saline solution and then packed before being used for the exchange transfusion (cf. Wiener and Sonn[11]).

Results

To date the authors have treated 22 erythroblastotic infants with exchange transfusion of packed cells. In two of these cases the disease was caused by sensitization to the A and B agglutinogen. Only two patients died, one a severely affected infant with hemorrhagic manifestations, referred for therapy in a moribund condition; this baby died only a few minutes after the completion of the transfusion. In the second case, death was not related to the primary disease; the baby died when 2 weeks of age from B. coli sepsis and meningitis.

TABLE 2

Mortality of Erythroblastosis Due to Rh Sensitization Following Treatment by Exchange Transfusion

Method of exchange transfusion	No. of patients treated	Mortality	
		No. of cases	%±P.E.
1. 500 cc. whole blood	38	9	23.7±4.6
2. 1,000 cc. whole blood	48	7	14.6±3.4
3. 120 cc. packed red cells	20	2	10.0±4.5
Totals	106	18	17.0±2.5

Table 2 is a summary of the authors' experience to date with the use of exchange transfusion for the therapy of typical cases of erythroblastosis due to Rh sensitization. The over-all mortality was 17% and there has been a progressive fall in the mortality rate from 23.7% to 10.0% in the three series of cases treated. However, these encouraging results cannot be accepted at face value for several reasons. Firstly, the maximum difference, 13.7%, is less than three times its probable error (6.4%) so that the deviation could be accidental. In addition, granting that the improvement is a real one, one might still argue that the cases in the three series were not comparable in severity. Finally, the drop in mortality rate has been one that could be attributed in part to increased skill in the general management of the cases. At any rate, one cannot deny that exchange transfusion with a smaller amount of packed cells is a relatively innocuous procedure, while exchange transfusion with 500 or 1,000 cc. of citrated blood is a fairly formidable operation. Some workers[12,13] have even encountered fatalities attributable to the latter procedure itself.

Two cases encountered during the present study will be presented in detail, not as further evidence of the value of the procedure, but because of their unusual clinical features. The following is the most severe case of erythroblastosis that the authors have treated successfully to date. The infant survived without sequelae despite a high maternal antibody titer, prematurity complicated by excessive weight loss, and severe clinical manifestations including the highest peripheral erythroblast count the authors have ever encountered, and deep and prolonged jaundice.

Case 1: The mother of this patient was referred in the 15th week of her second pregnancy because she had been found to be Rh-negative. Her first pregnancy had terminated 2 yr. before with the birth of a full term male who lived only 2 days. The baby was said to have had a fractured skull following a prolonged labor, which was complicated by the presence of an uterine tumor. Three months later the tumor was removed and the mother was given 2 blood transfusions. Whether she received Rh-positive or Rh-negative blood is not known.

At the time of the first visit the mother was found to belong to type O MN rh and the father to type O MN Rh_1rh. Tests for Rh antibodies on the prospective mother's serum at this time were negative. The tests were repeated at intervals throughout the remainder of the pregnancy with the results shown in table 3.

TABLE 3

RH ANTIBODY STUDIES ON MATERNAL SERUM CASE 1

Time of test	Titer of antibodies (units)		
	Agglutination technic	Albumin-plasma conglutination	Enzyme-treated cells
15 wk.	0	0	—
28 wk.	0	0	—
35 wk.	14	32	128
37 wk.	4	19	104
Postpartum (24 hr.)	Doubtful	72	224

It is clear from the table that the mother became sensitized to the Rh factor some time between the 28th and 35th week, and that the fetus was Rh-positive.* Accordingly, preparations were made for the delivery and treatment of an erythroblastotic infant. In view of the fact that the mother had already undergone gynecologic surgery, it was the opinion of the obstetrician that delivery could be most safely accomplished by cesarean section, and this was carried out at 38 wk. in order to limit the time that the fetus would be exposed to the action of the maternal antibodies.

At birth, the infant, a female weighing 2.2 kg., was seen to be pale and mildly jaundiced. She appeared to be weak, but cried when stimulated. Liver and spleen were not palpable. A blood count done immediately after birth showed: Hgb. 7.2 gm./100 cc.; RBC count 1.5 million/cmm.; WBC count 14.0 thousand/cmm.; differential: polymorphonuclears, 52 (8 band forms); lymphocytes, 40; metamyelocytes, 8; 2,800 nucleated RBC/100 WBC (100 early, 2,700 late).

In preparation for the treatment of this infant, 400 cc. of blood had been drawn from a nonsensitized type rh, group O, male donor into citrate solution and packed by centrifugation. The plasma was removed and the packed cells were used in the transfusion. The radial artery was exposed and bled in the usual manner, while the packed cells were introduced through the exposed saphenous vein at the ankle. To facilitate bleeding heparin 0.1 cc. (100 units) were given intravenously at the onset. Before the bleeding was started, however, 15 cc. of packed cells were introduced because of the anemia. Following this, 120 cc. of blood were removed from the radial artery while 125 cc. of packed cells were simultaneously introduced into the saphenous vein. The procedure was completed in 30 min. without incident, and the baby appeared to be in fair condition at its termination. Tests done subsequently on the cord blood showed that the baby belonged to group O, type MN, type Rh_1rh. Both the conglutination and antiglobulin tests for coating of the baby's cells were positive, and the cord serum showed a titer of free Rh antibodies of 5 u. against trypsinated cells. The icterus index of the cord serum was 48 u.

Seven hours after the procedure the blood count was repeated and now showed: Hgb. 16.6 gm./100 cc.; RBC count 6.1 million/cmm.; WBC count 35.0 thousand/cmm.; differential: polymorphonuclears, 80 (16 band forms); lymphocytes, 10; metamyelocytes, 4; myelocytes 6; 730 nucleated RBC/100 WBC (100 early, 630 late).

* Despite claims that an Rh-negative fetus can cause an "anamnestic" rise in the antibody titer of its sensitized Rh-negative mother, this has not occurred in 12 cases of this kind studied by the authors.[14]

TABLE 4

HEMATOLOGIC DATA IN CASE 1

	At birth	7 hr.	2 days	4 days	7 days	10 days	14 days	21 days	32 days	37 days		41 days	60 days	139 days
Hgb. gm./100 cc.	7.2	16.6	17.2	18.1	15.9	14.9	13.6	11.4	7.8	6.0		13.6	9.7	10.3
RBC (million/cmm.)	1.51	6.12	5.8	6.5	5.73	5.56	4.74	4.22	2.64	2.35		4.77	3.62	4.22
WBC	14,000	35,000	34,400	11,800	20,400	13,750	12,250	11,250	9,200	23,800		12,350	8,560	20,700
Polys	52	80	59	66	48	48	57	58	43	44		43	36	40
Bands	(8)	(16)	(16)	(14)	(3)	(4)	(3)	(3)	(8)	(5)		(8)	(2)	(3)
Lymphs	40	10	18	24	45	44	36	32	44	46		54	58	53
Myelocytes	8	10	21	6	5	5	3	3	8	3		3	0	0
Eosinophiles	0	0	0	1	0	1	2	2	2	2		0	2	2
Monocytes	0	0	1	3	2	2	2	5	3	5		0	4	5
Basophiles	0	0	1	0	0	0	0	0	0	0		0	0	0
Nucleated RBC (Early	126	100	8	3	1	1	0	1	3	3		2	0	0
Nucleated RBC Late)	2,700	630	225	15	4	2	0	2	1	5		4	0	0
Reticulocytes (per cent)	—	—	8	10	7	10	6	—	6	—		—	1	—
Icterus index	48	56	—	—	—	80	—	—	30	—		—	—	—
Percentage donor's blood	0	82	—	—	—	90	—	90	80	20		—	50	—

Transfusion—50 cc. Packed Orh Cells

Thirteen hours after delivery the baby's condition appeared to be good; she cried lustily and was responsive. Jaundice appeared to be about as intense as at the time of birth and the liver was now palpable 2 fingerbreadths below the costal margin on the right. The spleen was still not palpable. The temperature was 38.8°C. During the ensuing week the baby continued to have fever up to 39.4°C., but without any evidence of localized infection. Nevertheless, she was treated with penicillin, and her temperature gradually fell to normal by the end of the second week of life.

Jaundice increased, however, until by the end of the fourth day the baby appeared to be actually green. The liver and spleen were now both enlarged and firm. The baby was somnolent, ate rather poorly and lost 0.5 kg. down to 1.7 kg. The baby's poor condition prevented taking blood for the determination of the icterus index at its height, but when the child began to show some clinical improvement the icterus index was found to be 80 u. This was on the tenth day of life. The liver and spleen receded during the remainder of the hospital stay, but despite the falling icterus index which was down to 30 u. on the 32nd day the skin was still stained deep green. Weight gain did not commence until the end of the first month and was slow at first. The birth weight was regained by the 48th day and continued at a satisfactory rate from that point onward.

The course of the blood count during the hospital stay is summarized in table 4. Hgb. fell to 40% (6 gm.) on the 37th day and a transfusion of 50 cc. of packed cells was given at that time.

When seen again at the age of 10 wk. the baby weighed 3.2 kg. The color was good. The liver and spleen were no longer palpable, and the baby appeared bright and alert. She was last seen at the age of 8 mo. and no neurologic abnormalities were made out.

The second case to be described is also presented because of its interesting serologic and clinical features.

Case 2. This Negro family was referred because of the following obstetric history. The first baby, a girl, was born 4 yr. previously following a normal delivery. This child is normal today. The second pregnancy 2 yr. later, however, resulted after a full term normal delivery in the birth of a boy who was jaundiced at birth. The jaundice cleared without treatment after 12 days, but the baby failed to develop normally. He does not walk or talk, and cannot hold his head up. Although he has no athetosis, he appears to be unable to move his arms or his legs, and breathes with a continuous snore. The mother, at her first visit, was in the 37th week of her third pregnancy, and had been typed as Rh-negative elsewhere.

TABLE 5

RESULTS OF GROUPING AND RH-HR TESTS IN CASE 2

Blood of	Group and subgroup	M-N Type	Rh-Hr Type	Possible Rh-Hr genotypes
Father	A_1B	M	Rh_1rh	R^1R^0, R^1r or R^0r'
Mother	O	M	Rh_2rh	R^2R^0, R^2r or R^0r''
1st child	B	M	Rh_0	R^0R^0 or R^0r
2nd child (spastic)	B	M	Rh_1rh	R^1R^0, R^1r, or R^0r'

Grouping and Rh-Hr tests on the bloods of all members of the family gave the results shown in table 5. It is evident from the table that the previous report that the mother was Rh-negative was in error, and some other cause had to be found to explain the symptoms in the second child. Since the mother and both children were positive for the partial antigens Rh_0, hr′ and hr″ these could be ruled out as factors causing isosensitization in this case. No anti-rh′ antibodies could be found in the maternal serum, and tests for unusual antibodies were negative by the agglutination method as well as by the albumin-plasma, acacia, and enzyme-treated cells technics for the determination of univalent antibodies.

Since the mother belonged to group O while both children belonged to group B, the alpha and beta antibodies in the maternal serum were titrated. The results of these tests are shown in table 6. The tests showed that the mother was moderately sensitized to the B factor, and this is the probable explanation for the second baby's neonatal jaundice and subsequent neurologic manifestations. From the grouping tests on the father there was an even chance that the expected baby would belong to

either group A or group B, and it was planned that if the baby belonged to group B an exchange transfusion would be carried out in order to prevent a repetition of the outcome in the second child. It might be pointed out that since prediction of the development of symptoms of erythroblastosis cannot be made with the same accuracy in instances involving the A-B-O groups as in Rh sensitization, plans for use of exchange transfusion in this case were to be held in abeyance until such time as the expected infant exhibited manifestations of erythroblastosis (cf. Wiener et al.[15]).

At birth the baby was found to be jaundiced and a little pale. However, the authors were not notified of the birth until 12 hr. later, and tests were then carried out on the baby. His blood belonged to group B, type M, type Rh_o. Hgb. was 15 gm./100 cc. with RBC count 5.3 million/cmm. WBC count was 51.1 thousand/cmm. with 57 polymorphonuclears (9 of which were band forms),

TABLE 6

TITERS OF ALPHA AND BETA ANTIBODIES IN MATERNAL SERUM OF CASE 2

Antibody tested	Titration technic		
	Saline agglutination (units)	Plasma conglutination (units)	Acacia conglutination (units)
Alpha	40	35	160
Beta	60	320	960

24 lymphocytes, 1 eosinophile, 1 monocyte and 17 myelocytes. RBC showed some polychromasia, occasional spherocytosis, anisocytosis and poikilocytosis. There were 177 late erythroblasts/100 WBC on the smear and 9 early erythroblasts. The icterus index was 72 u.

Tests for free antibodies in the baby's serum showed that there were 3 u. of anti-A present by the albumin-plasma conglutination method, and 80 u. by the acacia conglutination method. No anti-A could be demonstrated by the saline agglutination technic and anti-B could not be demonstrated by any of these methods. Evidently, the anti-B had been absorbed into the baby's red blood cells, and this was the cause of the symptoms in the baby.

Accordingly, the baby was treated with a modified exchange transfusion using 120 cc. of packed cells from a group O Rh-positive donor. The procedure was carried out over a period of about 25 min. and the baby showed no untoward symptoms either during the transfusion or after its completion. The jaundice subsided rapidly and the baby was discharged with its mother on the fifth hospital day. A blood count done on the day of discharge showed Hgb. 16.8 gm./100 cc. with RBC count 5.7 million/cmm. There were 4 nucleated red blood cells/100 white cells on the smear. The subsequent course was uneventful.

SUMMARY AND CONCLUSIONS

A simplified method of treating erythroblastosis by exchange transfusion is described in which the patient is bled and simultaneously transfused with compatible packed red cells. A table is presented which gives the final hematocrit and percentage of inagglutinable red blood cells in the patient's body at the termination of the exchange transfusion, in relation to the patient's initial hematocrit and the amount of blood exchanged. An exchange transfusion with 100 to 150 cc. of packed cells appears to be adequate regardless of the severity of the anemia.

Statistical analysis of the result of 106 exchange transfusions shows a progressive drop in mortality rate from 23.7% in 38 cases treated with 500 cc. of whole citrated blood, to 14.6 cc. in 48 cases treated with 1,000 cc. of whole citrated blood, and to 10.0% in 20 cases treated with 120 cc. of packed cells. While the improvement may be accidental, there is no doubt that exchange transfusion with packed cells is a simpler procedure which avoids the introduction into the patient's body of large amounts of adult plasma, and potentially toxic doses of citrate and calcium. Two cases are described in detail which have unusual serologic and clinical features and illustrate the types of problems which may arise when treating erythroblastotic babies.

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SPANISH ABSTRACT

Modificación de la Técnica de Transfusión de Intercambio (Exchange Transfusion) en el Tratamiento de la Eritroblastosis Fetalis

Los autores describen una modificación de la técnica de transfusión de intercambio, consistente en el uso de glóbulos rojos concentrados en lugar de sangre citratada total. Las ventajas de este método consisten en la rapidez de la operación y en la eliminación de la mayor parte del plasma y citrato de la sangre total. Asímismo, se evita la necesidad de administrar calcio contra el efecto tetanigénico del citrato.

Los autores presentan una fórmula para calcular las cantidades de intercambio de sangre necesaria cuando este método es usado. Esta fórmula se basa en el volumen de sangre y hematocrito del niño, así como en el hematocrito de los glóbulos rojos concentrados usados en la transfusión y en el volumen de sangre intercambiada. Los autores presentan una gráfica tabulada construída con la ayuda de esta formula. De acuerdo con esta gráfica es evidente que la mayor eficacia de este intercambio de sangre depende del grado de la anemia del niño, es decir que aquellos niños seriamente afectados son los que más se benefician con este método. La cantidad de glóbulos concentrados ordinariamente usados en la transfusión es de 120 a 150 centímetros cúbicos.

Los autores comparan los promedios de mortalidad en tres series de casos. La mortalidad en el grupo de niños con eritroblastosis tratados con 500 cc de sangre total en la transfusión de intercambio fué 23.7% ±4.6%, en el grupo de niños en los cuales 1000 cc. de sangre total fueron usados la mortalidad fué de 14.6% ± 3.4%, mientras que en el grupo de niños tratados con los glóbulos concentrados en la transfusión de intercambio, la mortalidad fué de 10% ± 4.5%. Esta diferencia en los promedios de mortalidad no tienen ningún valor estadístico debido a el pequeño número de casos de la serie.

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AMERICAN ACADEMY OF PEDIATRICS, INC. PROCEEDINGS AND REPORTS

THE PRESIDENT'S PAGE

I AM sure that the greater part of our membership is not aware of the immense amount of productive work accomplished by our scientific committees.

Unfortunately I cannot comment on all of them because there is not space. I shall outline the composition and objectives of three of these committees which shall serve as examples. I was going to include the Committee on Education, but I will refer to that committee in a later letter.

The Committee on Immunization and Therapeutic Procedures has as its chairman John Miller of San Francisco. This committee is composed of nine pediatricians whose chief interest lies in the field of immunology. There are those interested in bacterial, viral, rickettsial, and other childhood diseases for which active or passive immunization has significance. Others are specialists in immune sera, vaccines, or other antigens, and still others in the public health aspect of contagious diseases. Together they have just finished the revision of the Red Book. It will soon be in your hands and you will realize when you see it the labor expended. It is not intended to be a text book but a concise and contemporaneous reference on what the committee regards as good standard practice.

Peter Danis of St. Louis is the chairman of the Committee on Hospitals and Dispensaries. This committee is also composed of nine child specialists, and each was chosen because he or she was particularly qualified to contribute a special knowledge in the differing areas of the care of the child in the hospital. The fields covered are hospital administration, hospital construction, research in a hospital, the pediatric teaching of the house staff, the pediatric teaching of nursing, the psychological care of the child, and the care of contagious diseases in a general hospital. This committee has already begun work on a manual similar to the one referred to above, which will be available to our membership and will contain standard practices of hospital care of the child above the age of the newborn.

As you know, the Committee on Fetus and Newborn publishes a manual covering hospital care in the early days of life.

The third scientific committee I am using as an example is the Committee on Mentally and Physically Handicapped Children. The chairman of this committee is George Munns

of Winnetka. In his group are pediatricians interested in the rehabilitation of the poliomyelitis patient, the congenital cardiac child, the neurological problem, the psychiatric case, and the child afflicted with cerebral palsy. One of the members is particularly conversant with programs of a state and national character in the care of the handicapped child. They plan to publish a short standard manual that will be of aid to the practicing pediatrician.

I have talked of only three of the Scientific Committees, of which there are 10, each attacking their problem in a manner that will not only help the membership but will also strengthen our leadership in the field of child health.

PAUL W. BEAVEN, M.D., *President*

Round Table Discussion

THE TREATMENT OF ASTHMA

WILLIAM P. BUFFUM, M.D., Providence, R.I., *Chairman;* HARRY L. MUELLER, M.D., Winchester, Mass.

GORDON MANACE, M.D., Toronto, and R. H. MCBRIDE, M.D., Sioux City, Iowa, *Secretaries*

HYPOSENSITIZATION IN ASTHMA

Chairman Buffum: The treatment of the patient with asthma is often a difficult and complicated problem. In this discussion we are concerning ourselves only with "hyposensitization," which is only a part and sometimes a very small part of the treatment.

Probably it is best to treat with all the inhalant allergens that are causing or seem likely to be causing symptoms. From the history and the tests it is decided which substances are important in a given case, and extracts of these allergens are injected regularly.

House dust is almost always given in perennial asthma. It seems to be the commonest trouble maker in the patients, and is usually used in treatment, unless the dust skin tests are negative and also something else is clearly indicated. Animal danders, for instance, are also used, when they seem to be a likely source of trouble, and when they cannot be completely avoided.

The pollens are used which by history and by skin test seem to be indicated. For instance, if a patient is worse in June and gives a positive skin test to grass pollen, grass pollen is given as part of the treatment. If, in addition he gives a good positive test to ragweed, and is not worse in September, ragweed should not be included in the treatment.

Molds undoubtedly play a part in some cases. Patients who have trouble in the summer may be sensitive to molds. Not uncommonly pollen patients whose treatment is not successful are found to be sensitive to molds also. Alternaria is much the most important of these, with hormodendron a poor second. There are several other molds which may be important in a given case. A patient who has trouble in the summer, and who has positive tests to one of these molds, should have that mold included in his treatment.

If the patient has had symptoms limited to the ragweed season, and if our treatment is started well before the season, our problem is relatively simple. We start treatment with a dilution of ragweed that we know by experience will be safe with this patient, and give injections once or twice a week increasing the size of the dose each time.

One good way to start is to do a series of i.c. tests with different strengths of ragweed, and start treatment with the solution that just gives a positive test. This is conservative treatment, as most patients will tolerate larger doses.

Unless the patient is unusually sensitive, the dose can be doubled each time for the first 6 or 8 doses. It must be carefully noted that there are no systemic symptoms, and no local reaction causing appreciable discomfort. For the remaining doses, about a 50% increase is good for the usual patient, but one is governed by the reaction.

From personal experience I cannot say what is the best top dose. Most allergists like to get the top dose up to about 5,000 to 10,000 noon units or 0.25 to 0.5 cc. of the 1/50 extract, depending partly on the concentration of pollen in the air. With the occasional very sensitive case, they consider a smaller dose just as satisfactory. Hansel claims that much smaller doses are just as satisfactory, and many others are now using smaller doses. From my own experience with children with asthma, I have not been able to see that it is necessary to reach the large top dose. These injections can be continued once a month throughout the year.

The co-seasonal treatment in asthma is usually less effective than preseasonal treatment, but is likely to be helpful. The immunologic mechanism involved in co-seasonal treatment is not clear, but, as a working hypothesis, we can consider that we are stimulating the production of blocking antibodies, and yet giving a dose not large enough to overburden the patient with his allergen.

From the Annual Meeting of the American Academy of Pediatrics, Chicago, Oct. 17 and 18, 1950.

Vaughan, Hansel and others have described methods of co-seasonal treatment, and these methods have a good deal in common. Treatment is given with a dilution of the allergen that just causes a positive i.c. test. These injections are started at daily intervals, or, if relief is obtained, the interval may be governed by the duration of the relief.

Some relief should be obtained usually after the first dose, at any rate after 3 or 4 doses. If no improvement occurs, the treatment is probably wrong, but sometimes for no explicable reason, the co-seasonal treatment does not work.

Severe and moderate perennial asthma is treated best by the co-seasonal method. Some system of serial intracutaneous testing may be used, with 1, 2 or 3 of the allergens which are most important in the particular case, to determine the initial dose.

One may use 0.1 cc. of the solution with which a weak positive intracutaneous test was obtained. It is of vital importance that the injection should not make the patient worse; if this happens, the dose was excessive. Usually the second dose should be given within a day or 2.

Improvement should be noted after 1, 2 or 3 injections. If this does not occur either the treatment is wrong or other factors, such as infection, or food allergy, or emotional distress, should be inquired into. In respect to the injections alone, it has seemed to me that failure has been not uncommonly due to overdosage; and my first experiment in such cases is to cut down the dosage to below the dilution which gave a weak positive i.c. test.

Usually when a dosage is found which will cause improvement, after the first few days the dose may be increased by 50% each time. After the patient is doing well, it is probably best to continue to increase the dose for a while, but what is the optimum dose for a given antigen in a given patient is not known.

We see a small number of patients, usually those with severe chronic asthma, in whom it is very difficult to get improvement. In hyposensitization these patients sometimes do best on exceedingly small dosage, well below that which has been described.

After 4 or 5 injections have been given, an interval of 3 weeks between injections seems to be as good as a shorter interval, and later 4 weeks seems to be a satisfactory period.

Treatment of Infectious Asthma

Dr. Mueller: This summary is necessarily limited by space to the consideration of the treatment of infectious asthma. Although there are claims that infection does not act as an allergen in causing asthma but is merely a precipitating factor preparing the way for other allergens, the high familial background of allergy in these patients, the marked association of infectious asthma with other allergies, the high eosinophilia in both blood and mucus secretions and the reproduction of the asthmatic response by doses of vaccine all offer proof of bacterial allergy.

Since symptomatic treatment is not a part of this discussion, only etiologic therapy will be considered under the following headings:

I. Chemo- and Antibiotic Therapy. Immediate treatment involves their use for the presenting asthmatic attack and the choice of drug to be used should be decided on the indications for that particular infection. For this type of treatment the value of your knowledge as a pediatrician outweighs the value of your knowledge as an allergist. Possibly the only difference between using these drugs in the nonallergic and the allergic child is the fact that in the latter you would be more prompt to use them because of the complicating factor of asthma. Prophylactic treatment with chemotherapy is effective in preventing many bacterial infections but has the disadvantages of gradually losing its effect, requiring a regular daily task of taking the medication, close clinical and laboratory supervision and adds the possibility of sensitization or toxicity. If used, dosage of 0.5 gm. of the combinations of the sulfonamides given twice daily for a child of 50 to 70 lbs. is effective and appropriate. Penicillin by mouth prophylactically is a better choice since the possibility of toxicity and need for close supervision are less but its effect still has a tendency to diminish with time. Dosage of 100,000 u. 3 times daily for a child of 50 to 70 lbs. is recommended. Its use by injection is no more effective and this method has the disadvantages of discomfort and expense. Similar use of aureomycin, chloromycetin and terramycin are equally effective but the additional expense has not yet been justified by reported superior results. The toxic effects of streptomycin preclude its use prophylactically. Antibiotic therapy by the aerosol method has a place in the group of patients having chronic pulmonary suppuration and bronchiectasis complicating their asthma. If employed, aerosol treatment should be done with good effective apparatus such as that described by Finke or Segal or with an oxygen tank.

II. If the treatment of allergies due to infection were to follow along the lines of the most successful treatment of other allergies, then aside from avoiding the antigen itself, hyposensitization by in-

jection of the antigen should offer the best method. Vaccine therapy prophylactically does give the best results in the average case, and is easily coordinated with the other inoculation treatment so frequently being given to these patients. Stock vaccines are recommended on the theory that they give "better coverage" than antogenous vaccines do in the great variety of respiratory infections encountered in children. It has been shown that during the course of one infection cultures at intervals may obtain entirely different organisms. After determining a starting dose by testing with various dilutions, then gradually increasing weekly doses until a local reaction results, followed by doses of that size at 3 to 4 week intervals on a perennial basis is a satisfactory routine. General reactions, although uncommon, are usually delayed, and any such occurrence is an indication for decreasing the dosage.

III. Radium and roentgenographic treatment to the lymphoid tissue of the nasopharynx is a valuable method in the severe and intractable cases that do not do well with the preceding therapy. In some patients there is a strikingly beneficial result. Asthma due to other allergens should be brought under control before this method is used. Further selection is made, based upon the presence of hypertrophied lymphoid follicles in the nasopharynx and/or evidence of infection by the presence of hyperemia and exudate. In determining this, an examination and opinion by an otolaryngologist is invaluable. A series of 3 treatments is given and if indicated this is repeated once within a period of 6 to 12 months. The mechanism which affords relief is unknown but with this treatment the lymphoid follicles melt away and in so doing, probably eliminate foci of infection. Other factors that may play a part are (1) lessening of secretions, (2) reduction of mechanical obstruction, (3) changes in bacterial flora and (4) the theoretic possibility of increasing the threshold of absorption for allergens.

IV. The elimination of foci of infection should not be neglected as a method of treatment. This is perhaps a less important factor in children than in adults but adenotonsillectomy should be performed for the same indications as are used in any patients. Indiscriminate use of this operation is not warranted by results.

Dr. Park A. Bradshaw, Muskegon, Mich.: Aren't you more apt to get systemic reactions with the first 3 or 4 doses that you give?

Chairman Buffum: I have had systemic reactions with the first dose, but not frequently with the second, third or fourth.

Dr. Bradshaw: I have been scared enough so that I have been repeating my first dose 3 or 4 times before I start going up. I stopped getting trouble.

Chairman Buffum: You may get better results that way. I believe that if I get systemic reactions with my first doses that I am definitely starting with too strong a dose.

Dr. Bradshaw: Suppose I didn't get it on the first dose but the second dose, am I building up a reaction there? I am not doubling it, just raising it 50% each time.

Chairman Buffum: The effect is not supposed to be cumulative unless the injections are less than 3 days apart.

Dr. J. R. Schroder, Janesville, Wis.: Over how long a period of time, hours or days after giving a shot, do you feel reaction may be attributable to the antigen?

Chairman Buffum: Serious constitutional reactions are within 15 minutes. A systemic reaction may occur within 12 hours or even later.

Dr. Roy N. Andrews, Mankato, Minn.: It has been our experience never to have our reactions early. Our reactions come when they are pretty much up the ladder in dosage.

Dr. Harold J. Friedman, Boston: It is our duty to perform certain tests for diagnostic purposes. I use the scratch test. However, I generally refer my patients to an allergist and, if I can, to a pediatric allergist. Even in the hands of an allergist, my patient is liable to come down with an acute attack of asthma in the middle of the night; I have to make that call and I am concerned how we are going to handle the acute phase of the asthmatic attack at home.

Chairman Buffum: We will go into that in detail later, but may I say something about the question of sending the patient to an allergist. I think, as to the pediatrician treating these cases, it depends almost entirely on whether he is willing to give the time and effort to do it. You have to go into a lot of detail. If you are a pediatrician with all kinds of patients to keep you busy, then you may prefer to send those cases to an allergist.

Dr. Friedman, Boston: I started with these patients but with the type of work required I found I had to make a choice between going into pediatric allergy or being a pediatrician, and I prefer pediatrics.

Dr. Mueller: I think the situation is a little different with many pediatricians who are practicing in smaller communities. They must of necessity familiarize themselves with these procedures in order to carry on with their patients practically.

Question: Do either one of you care to give figures that indicate the percentage of good results in the treatment of asthma, leaving hay fever out of the picture?

Chairman Buffum: We looked up the cases in the allergy clinic at the Rhode Island Hospital and about 65% showed good results. By good results, I mean that the patients were not completely "cured" but entirely or nearly entirely relieved.

Question: When you state that there is a percentage of relief from the antibiotics, do you mean that you use these prophylactically with the vaccine?

Dr. Mueller: No, if we are using vaccine, we use the antibiotics only for the immediate control of intercurrent infections.

Dr. Maurice T. Briggs, Lynn, Mass.: I am interested in the child who vomits after he has had an attack. Is it the result of the asthma or the drug medication?

Dr. Mueller: It is frequently the drug.

Question: Don't you get patients who vomit when they have infection and yet have no allergy at all? They are children who are liable to vomit with any physiologic upset.

Dr. Mueller: Yes, you do run into those same children with asthma. But medication is frequently the cause of vomiting.

Chairman Buffum: Some of these children have cyclic vomiting and asthma at the same time. They may develop dehydration and collapse rapidly. If a patient is vomiting and seriously troubled with asthma, it should not go too far before he goes to the hospital and gets intravenous fluid. We had a patient die at the hospital an hour after he was admitted with asthma, vomiting and dehydration.

Dr. Edwin A. Harper, Lynchburg, Va.: You have spoken of treating with pollen, molds and house dust. Were you limiting yourself for this particular study, or do you use such incidentals as kapok and animal hair fairly commonly? Do you use those in the pollen mixture?

Chairman Buffum: Yes, I use animal hair and kapok not uncommonly. Great care is taken to be sure that the solution is not too strong. Kapok especially is a dangerous antigen. I use them in the same syringe or in the same bottle with the pollen extract or house dust.

Dr. Mueller: As far as kapok, common hair, etc., are concerned, house dust is actually a mixture of all these things.

Question: What about the negative test to wool? How do you feel about the ordinary cotton blanket on the bed?

Chairman Buffum: Every case of asthma I consider possibly sensitive to wool.

Dr. Mueller: If your patient has symptoms related to wool, regardless of what the skin tests show, you should treat the patient by removal of wool.

Dr. Carl Zelson, New York City: Have you had any cases where all the skin tests have been negative?

Chairman Buffum: Yes.

Question: The influenzal vaccine, the virus vaccine, has not been discussed. I would like your opinion on that.

Chairman Buffum: I should use it in the presence of an influenza epidemic only and should do an intracutaneous test first.

Question: What method of injection would you use in the vaccine therapy?

Dr. Mueller: Subcutaneous.

Question: What dosage of x-ray do they use in radiation therapy?

Dr. Mueller: Radium 100 mg. for 8 minutes.

Dr. James H. Root, Jr., Waterbury, Conn.: Can you use the same syringe for your innoculation of your cold vaccine and your other allergens?

Dr. Mueller: We don't use the same syringe. The vaccine dosage is usually so large that it would not be practical

Dr. Root: Can you explain the mechanisms by which the patients sometimes get much worse after their teen age?

Dr. Mueller: I can't explain that.

Dr. Root: No one has said anything about the psychologic aspects of asthma.

Dr. Mueller: We don't have the time here to go into that, but I think it is extremely important.

Dr. Zelson: What about the use of ACTH?

Dr. Mueller: We are not using it at present in a disease which we believe can be satisfactorily controlled by other methods. It has been used in small doses for an acute attack, but that is not getting at the base of the trouble.

Chairman Buffum: I have not used it yet, but would do it if an attack threatened to be dangerous and could not be promptly relieved by other measures in the hospital.

THERAPY OF INFECTIOUS DISEASES

A Symposium

WALDO E. NELSON, M.D., *Chairman*
St. Christopher's Hospital for Children, Philadelphia

RESISTANCE TO INFECTIONS

(Abstract not available)

COLIN M. MACLEOD, M.D.
New York University College of Medicine, New York City

THE PLACE OF PROPHYLAXIS IN THE CONTROL OF INFECTIOUS DISEASE

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MECHANISMS AND INFLUENCE OF BACTERIAL VARIABILITY ON SEVERITY OF INFECTIONS AND THEIR RESPONSE TO SPECIFIC THERAPY

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SELECTION OF ANTIBIOTICS

(to be published in PEDIATRICS as an Original Article)

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THE ROLE OF STEROIDS IN INFECTION AND IMMUNITY

MAXWELL FINLAND, M.D.
Harvard Medical School, Boston

Presented at the Annual Meeting of the American Academy of Pediatrics, Chicago, Oct. 19, 1950.

INTRODUCTION

WALDO E. NELSON, M.D.

A word of explanation may be in order in regard to the nature of the program arranged for this panel, since its pattern deviates somewhat from those usually arranged for clinical meetings.

In recent years the introduction of new antimicrobial agents has occurred with such rapidity that emphases have been principally upon which pathogenic organisms were susceptible to the various agents and upon the ranges of effective dosages, the routes of administration and the untoward reactions. Details of acceptable plans of usage of the various therapeutic agents are now common knowledge and are also readily available in the medical literature and in brochures published by the pharmaceutical houses. Other, and as yet unknown, antimicrobial agents will continue to appear and make it necessary for the clinician to be even more discriminating in his selection of therapy than is the case at the moment.

Perhaps of equal importance with the selection of a therapeutic agent is the decision as to whether any artificial assistance is required for the control of a particular infection. If one understood the relationship between the host and a pathogenic parasite at a given moment, he would be in an extremely favorable position to decide whether therapeutic assistance was indicated and even to decide more exactly the nature of that assistance—a clinical utopia.

This program was planned with the idea that those of us whose activities are principally clinical might gain some insight into the thinking and the accomplishments of those who are trying to find out more about the host-parasite relationship and what can be done to help the host control and conquer or live with the pathogenic invader.

THE PLACE OF PROPHYLAXIS IN THE CONTROL OF INFECTIOUS DISEASE

T. F. MCNAIR SCOTT, M.D.

Prophylaxis will be considered in the broad framework of this symposium—namely, host-parasite relationship. Ideal prophylaxis may be considered as a state in which the parasite enters its host with the minimum of defense reaction on the part of the latter—just enough to produce antibodies that last the life of the host. In certain categories of infection such as the respiratory virus diseases, no immunity is demonstrable after infection and in these, prophylactic control must fall short of ideal.

We can review the various forms prophylaxis can take as follows:

I. Control of Environment.

a. Destruction of the parasite directly.

1. Disinfection procedures. These include sterilization and pasteurization. Success of this type of prophylaxis depends on technical perfection, and technical failure can lead to disaster.

2. Air disinfection. Ultraviolet light, bactericidal chemicals—e.g., triethylene glycol—under certain circumstances, such as overcrowded barracks, can play a role in control of infection. As an adjuvant, technics for control of dust, e.g., oiling of blankets, may play an important part in wards and operating rooms. Certain respiratory diseases, such as the common cold, are spread more by contact rather than air and would not be affected. Furthermore, the prevention of such truly airborne diseases as rubeola and varicella during childhood may be considered detrimental.

3. Hand washing and gowns. The importance of contact in the spread of disease emphasizes the simplest but sometimes the most neglected prophylactic measure.

b. Elimination of essential intermediate host.

Such parasites that require an intermediate host, such as plague bacilli, rickettsia of typhus and arthropod-borne encephalitic viruses or the virus of yellow fever, can be largely controlled by eliminating the intermediate host or vector.

c. Interposition of barriers between host and parasite.

1. Mosquito nets and insect repellents have proved valuable.

2. The face mask. This has limited value and it may actually be detrimental because it induces fingering.

d. Avoidance of parasite.

Isolation plays an important part in immediate control. However, prolonged isolation followed by accidental exposure leads to disastrous consequences, e.g., rubeola in the Faroe Islands.

II. Changes Induced in the Host.

a. Use of drugs.

The wide-spread use of antibiotics have a prophylactic effect in preventing secondary bacterial complications in many diseases. However, indiscriminate use may be injurious through the development of resistant organisms.

b. Immunization.

1. Passive. The introduction of preformed antibodies has a well known but limited value.

2. Active. The introduction of the parasite, either killed or rarely living, stimulates the host to produce his own defenses. However, booster doses are necessary.

3. Passive active. Where it is possible to introduce the active living agent during a period of waning passive immunity, the host can produce his own defenses and yet be safe from too violent a first contact with his parasite. This is the ideal approach.

c. Nonspecific changes in host physiology.

This is a relatively unexplored field but may be a powerful factor in prophylaxis.

III. Changes in the Parasite.

a. Killing.

The use of killed agents is widespread and valuable.

b. Modification.

1. Attenuation. By passing the living parasite through a less susceptible host, it may be less virulent for its natural host and thus be used for immunization. Tissue culture yellow fever vaccine is an example.

2. Mutation. The vaccine virus used for vaccination is probably a mutant of smallpox virus.

All these methods of prophylaxis have their place, but we should strive when possible to induce the ideal prophylaxis which is that achieved by recovery from inapparent infection with an agent that produced lifelong immunity.

MECHANISM AND INFLUENCE OF BACTERIAL VARIABILITY ON SEVERITY OF INFECTIONS AND THEIR RESPONSE TO SPECIFIC THERAPY*

HATTIE E. ALEXANDER, M.D., AND GRACE LEIDY, A.B.

During the past 5 years evidence has been gathered on 2 important mechanisms which, taken together, provide an answer to a number of questions raised by clinical experience: (1) The mechanism responsible for increased resistance to antibacterial agents and (2) the forces which direct the virulence of organisms. Both are factors in bacterial variability.

There is now convincing evidence that increased resistance of many organisms to a number of antibacterial agents results from selective survival of spontaneously occurring resistant mutants.

Certain therapeutic implications are apparent and can, if applied, be expected to contribute to maintenance of the value of antibiotics.

In severe infections, in which presumably the bacterial population is large, there are clear indications for employing simultaneously the combined action of at least 2 effective agents which act through different mechanisms; under these circumstances the mutants resistant to one will be sensitive to the other; this criterion has been used in selecting the antibacterial agents to use in conjunction on the premise they must work through different mechanisms. For example, penicillin and sulfadiazine would be suitable for pneumococcus, streptococcus and meningococcus infections, and for the colon bacillus group the combined action of streptomycin and a sulfonamide. Aureomycin, chloromycetin and terramycin have been shown to operate through a mechanism differing from that of penicillin and streptomycin. Therefore they can replace sulfadiazine as an adjunct to either penicillin or streptomycin. In fact, recent results suggest that chloromycetin may be capable of replacing streptomycin in some severe infections. The available information suggests that 2 agents effective against a given organism act through different mechanisms when spontaneous mutants resistant to one are sensitive to the other.

Antibacterial agents should be reserved for treatment of infections for which there are clear indications of their need; the initial dose and duration of administration should aim to eliminate the

* The work reported here was supported by grants from the Commonwealth Fund and the National Institutes of Health.

infecting organisms as rapidly as possible by aiming for bactericidal concentrations over a sufficient period; this is possible even for penicillin. The concentrations of streptomycin, aureomycin and chloromycetin needed to kill gram-negative bacilli are known.

The indiscriminate use of antibacterial agents in the usual prophylactic doses is, in general, contraindicated.

Evidence was presented to show that the inherited characteristics of bacteria and therefore their virulence are directed by highly specific desoxyribonucleic acids which behave as genes. The important discovery by Avery, MacLeod and McCarty that pneumococcus virulence is controlled by a highly specific desoxyribonucleic acid was summarized and new data were presented to show that the type specificity and virulence of H. influenzae are also directed by a desoxyribonucleic acid fraction isolated from the type of H. influenzae desired. The transforming activity of this fraction was rapidly destroyed by a crystalline desoxyribonuclease. These results suggest that nontypable H. influenzae may be transformed into type b in the nasopharynx under the influence of suitable stimuli.

The hypothesis is advanced that a change in the hereditary traits of nonpathogenic strains of bacteria, brought about by desoxyribonucleic acids of unknown origin, may play an important role in epidemics.

Observations on the mode of action of desoxyribonucleic acid were presented.

THE ROLE OF STEROIDS IN INFECTION AND IMMUNITY

EDWARD H. KASS, PH.D., M.D.,* AND MAXWELL FINLAND, M.D.

The relationship of the hormones of the adrenal cortex to resistance to infectious disease has been re-examined as a result of the demonstration that patients with a wide variety of inflammatory and neoplastic disorders may be benefited by administration of cortisone and ACTH. The administration of ACTH to patients with pneumococcal and viral pneumonias was followed by prompt subsidence of fever with relief of symptoms and signs of toxemia. In patients with pneumococcal pneumonia bacteremia, rusty sputum containing many pneumococci and signs of consolidation persisted for several days. In some instances ACTH appeared to have induced a crisis; in others the fever returned while the patient was receiving the drug, only to disappear again when the dose of drug was increased. Extension of the lesion and the development of empyema occurred in one instance. There was no evidence of bactericidal effect exerted by the adrenocortical hormones, and antibodies appeared at the anticipated time with no clear indication of acceleration of their release or of delay in their appearance.

The literature contains data which are useful in interpreting the significance of these observations. Adrenalectomy uniformly increases the susceptibility of experimental animals to a wide variety of toxic and infectious agents, and this has its clinical counterpart in patients with Addison's disease. Adrenalectomy probably does not alter antibody formation, complement formation or acquired immunity, although the function of macrophages and other phagocytes seems to be decreased.

The administration of adrenocortical extracts (ACE) to adrenalectomized animals tends to reverse the effects of adrenalectomy, but the results are difficult to evaluate because of the varying potencies of different extracts. Clinical results using such extracts are open to considerable question in many instances, and even in such conditions as diphtheria and in the Waterhouse-Friderichsen syndrome clinical studies have been, on the whole, rather poorly controlled.

ACE administered to intact experimental animals has given slight but variable protection in a small number of infections, but in other experiments even with similar infections, no protection has been observed. In our studies large doses of ACTH or cortisone failed to increase significantly the resistance of mice to pneumococcal or influenza viral infections.

Although there are several experiments to the contrary, the weight of evidence in the literature indicates that ACTH and cortisone either have no effect on antibody formation, or may, after continued administration of the hormones, diminish antibody and gamma-globulin levels. The anamnestic response, initially thought to be related to adrenocortical activity, has been stated by others not to be related to adrenocortical function.

From the Thorndike Memorial Laboratory, Second and Fourth Medical Services (Harvard), Boston City Hospital and the Department of Medicine, Harvard Medical School, Boston.

Some of the studies mentioned were aided by a grant from the U. S. Public Health Service.

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In many infectious diseases, adrenocortical insufficiency may be present, as evidenced by histologic studies in fatal cases. However, in clinical studies such insufficiency has not been demonstrated, and in some instances evidence suggesting adrenal hyperactivity has been demonstrated during infections.

Some of the physiologic effects of ACTH which may be pertinent to the study of acute infections were summarized. ACTH is a potent antipyretic. The hormone has no effect on the susceptibility of mice to acute toxemia induced by influenza virus or by rickettsiae. Hypersensitivity is reduced by ACTH or cortisone, but the weight of evidence suggests that the effect is a nonspecific one on the inflammatory response and not a direct one on antigen-antibody combinations. Acute anaphylaxis is not affected by cortical hormones, nor is the reaction to histamine decreased. However, the more delayed cellular responses to antigenic stimulation are generally diminished if the dose of hormone is large enough; this diminution may simply reflect the effect of the hormones on the cellular phases of inflammation. Hyaluronidase activity is decreased by ACTH and cortisone, but the role of hyaluronidase in infection is difficult to evaluate and variable.

Ascorbic acid has been implicated in resistance to infection. Although ACTH decreases adrenal ascorbic acid, it has relatively little effect on blood levels of the vitamin. Scorbutic individuals excrete normal amounts of corticoids and have normal responses of their circulating eosinophiles to ACTH. Ascorbic acid has been claimed to alter the clinical course of rheumatic disorders, but the administration of large doses of ascorbic acid does not alter the eosinophile counts, and there is no evidence that ascorbic acid stimulates adrenocortical function.

In summary, there is inadequate knowledge of the function of the adrenocortical hormones, and insufficient knowledge of the physiology of infectious disease. Evidence that adrenocortical insufficiency occurs in infectious disease is fragmentary and there is sufficient evidence indicating adrenal activation in infections to make it likely that adrenocortical insufficiency is a rare complication of acute infections. The undesirable side effects of the hormones and the possibility that acute inflammatory responses may be diminished make it essential that the use of ACTH and cortisone in acute infections be undertaken with great caution. The hormones are not a substitute for antibiotic treatment, and are primarily investigative tools of great interest, but not warranting general use in the treatment of infectious disease.

THE HANDICAPPED CHILD

A Symposium

M. A. PERLSTEIN, M.D., CHAIRMAN

CLINICAL CORRELATION BETWEEN ETIOLOGY AND SYMPTOMATOLOGY IN CEREBRAL PALSY

M. A. PERLSTEIN, M.D.
Northwestern University Medical School, Chicago

DEVELOPMENTAL DIAGNOSIS IN CEREBRAL PALSY

ARNOLD GESELL, M.D.
Yale University, New Haven, Conn.

PREVENTION OF DEFORMITIES IN NEUROMUSCULAR HANDICAPS

(Abstract not available)

JOHN POHL, M.D.
Minneapolis

REVASCULARIZATION OF THE BRAIN

(Abstract not available)

CHARLES F. MCKHANN, M.D.
Western Reserve University School of Medicine, Cleveland

FACILITIES AND PROGRAMS FOR AID TO THE HANDICAPPED

MISS JANE SHOVER
National Society for Crippled Children and Adults, Inc., Chicago

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Presented at the Annual Meeting of the American Academy of Pediatrics, Chicago, Oct. 18, 1950.

CLINICAL CORRELATION BETWEEN ETIOLOGY AND SYMPTOMATOLOGY IN CEREBRAL PALSY

M. A. PERLSTEIN, M.D.

There is a great deal of correlation between the various types of clinical pictures seen in cerebral palsy and the etiologic factors. Thus there are certain noxae which have a predilection for certain portions of the brain. Anoxia tends to attack the extrapyramidal tract system, whereas hemorrhages tend to attack primarily the pyramidal tract.

Thus, one can often prognosticate on the basis of history the clinical pictures which are found. A classification of the various types of cerebral palsy can thus be based either upon an etiologic basis or upon a clinical basis.

Some Clinical Common Correlates in Cerebral Palsy

Where history is:	Common neurologic sequela is:
1. Prematurity	Spastic paraplegia
2. Breech delivery	Athetoid or spastic paraplegia
3. Toxemia of pregnancy	Spastic hemiplegia
4. Birth trauma	Spastic quadriplegia
5. Anoxia	Athetoid
6. Rh factor	Athetoid with deafness and paralysis of supraversion
7. Maternal rubella	Spastic with deafness or auditory aphasia, cataract, congenital heart
8. Precipitate or cesarian	Spastic quadriplegia or rigidity

DEVELOPMENTAL DIAGNOSIS IN CEREBRAL PALSY

ARNOLD GESELL, M.D.

The concept of development has far reaching implications in the diagnosis and the care of the handicapped child. Every infant, whether normal or handicapped, is confronted with the task of achieving his allotted measure of maturity. We cannot understand him unless we know something of his growth potentials.

For this reason, a considered developmental approach is desirable in our clinical procedures and treatment policies. Such an approach needs to be implemented, if it is to go beyond a mere philosophic attitude.

It should be pointed out that a developmental examination of an infant's behavior is not a psychometric I.Q. test. It is a more comprehensive observation of the total maturity status of the child, as manifested by diverse types of behavior patterns—motor, language, adaptive and personal-social.

To the infant the various test objects are so many toys which he exploits by eyes, hands and mouth. To the examiner the behavior tests are devices by which he elicits for careful inspection the maturity and the organization of the child's action system. In cases of cerebral palsy each behavior test becomes a diagnostic tool for detecting and defining neurologic deviations. A developmental type of behavior examination is especially effective for detecting, in infancy, slight but unusual deviations in eye-hand coordination and atypical exploitation patterns, which indicate a minimal type of cerebral injury.

In clinically experienced hands, a developmental behavior examination conducted formally, with precision of purpose, serves 5 functions as follows: 1. It ascertains stages of maturity and rates of development in infant and child, both normal and handicapped, 2. It yields an analytic diagnosis of the normal, defective and deviant aspects of the action system, 3. In minimal cerebral injury it may bring to early light otherwise unrecognized neurological impairments, 4. It sets up a life situation which renders objective information as to emotional stability, personality structure and parent-child relationships, 5. It implements a periodic type of developmental supervision, focussed upon the interpretation and guidance of the growth potentials.

FACILITIES AND PROGRAMS FOR AID TO THE HANDICAPPED

JAYNE SHOVER

Reaching our common goal of medical and allied care for the estimated 750,000 to 1,000,000 orthopedically handicapped requires teamwork of the highest quality among agencies and individuals concerned. Services to meet a part of this need have been set up by the Crippled Children's Services in the United States Children's Bureau, the United States Office of Education, the Office of Vocational Rehabilitation and the Veterans' Administration. These services come down to the local level through state departments of health, education and welfare; state schools, hospitals and institutions for the handicapped; state employment offices; and public schools and county and city health departments.

Voluntary agencies make an additional important contribution. Flexible and adaptable to varying community needs, they bring the problem to public attention ,and promote the research and experimentation essential to forward-looking programs. Among the national private, nonprofit agencies concerned with the physically handicapped are: the National Society for Crippled Children, National Foundation for Infantile Paralysis, American Heart Association, American Cancer Society, American Hearing Society, National Epilepsy League, and the National Tuberculosis Association. Those with particular concern for the orthopedically handicapped are:

1. The National Foundation for Infantile Paralysis, which provides emergency epidemic aid in poliomyelitis, medical and surgical care, hospitalization, nursing, physical therapy, orthopedic appliances, transportation of patients to clinics, supply of equipment to hospitals, and funds for personnel training and research.

2. The National Society for Crippled Children and Adults, the Easter Seal Agency, is a nationwide federation of more than 2,000 state and local member societies. Included in its program are special diagnostic clinics; medical and convalescent care; physical, occupational and speech therapy; cerebral palsy services; special teaching in crippled children's classes, and in homes, hospitals and convalescent care institutions; recreation; curative and sheltered workshops; employment placement; social service; and provision of prostheses, appliances and equipment.

Highlights of the Cerebral Palsy Program of the National Society in 1950 indicate that (1) largely as a result of this program, the number of cerebral palsy centers in the United States has grown from 16 to over 200 in 4 years, (2) the Easter Seal agencies have spent approximately $8,000,000 on cerebral palsy since 1946, including one third of a million dollars in scholarships for personnel training; and (3) the number of physicians with special training and experience in cerebral palsy has increased from 10 to 150 in 4 years.

The Cerebral Palsy Division provides consultation by specialists in organizing facilities for the care, education and rehabilitation of the cerebral palsied. Constant guidance is secured from liaison officers from the American Medical Association, the American Academy for Cerebral Palsy, the American Academy of Pediatrics and other medical and specialty groups. The Society also works in cooperation with physicians and other public and private agencies in program development.

Volunteer efforts are basic to the effective operation of the cerebral palsy program of the National Society. Many organizations, clubs, fraternal and civic groups have sponsored or cooperated in special projects on national, state and local levels through the National Society, in addition to the generous expenditure of time and effort by individuals.

It is the earnest desire of the National Society for Crippled Children and Adults to be of every possible assistance to pediatricians. Its comprehensive library of books, pamphlets and reprints, as well as its library of film slides and photographs, are available for lectures and exhibits. The bimonthly Crippled Child magazine publishes articles contributed by medical specialists and authorities in many fields serving the crippled.

Professional consultants on the staff of the National Society can be helpful in planning new services or extension of existing facilities. An extensive list of resources for the handicapped is available to assist in referral of various types of cases. Pediatricians are asked to join with the National Society in recruiting capable young men and women for professional training, and to refer them to the National Society for Crippled Children and Adults, 11 S. LaSalle St., Chicago, for advice and consultation regarding the many opportunities available in the professions.

ORAL HEALTH IN PEDIATRICS

A Symposium

JOHN A. BIGLER, M.D., *Chairman*

INTRODUCTION TO ORAL HEALTH IN PEDIATRICS

JOHN A. BIGLER, M.D.
Children's Memorial Hospital, Chicago

THE RESPONSIBILITY OF THE PEDIATRICIAN IN RELATIONSHIP TO ORAL HEALTH IN PEDIATRICS

ARTHUR ANDERSON, M.D.
Cornell University, Ithaca, N.Y.

DENTAL DISEASE AND ITS EFFECT ON THE ORAL MECHANISM OF THE CHILD

J. R. BLAYNEY, D.D.S.
University of Chicago School of Medicine, Chicago

MALOCCLUSION—ITS EFFECT ON THE ORAL MECHANISM

JOHN R. THOMPSON, D.D.S.
Northwestern University Dental School, Chicago

MANAGEMENT OF PROBLEMS RELATING TO THE DENTAL CARE OF THE CHILD

GEORGE W. TEUSCHER, D.D.S.
Northwestern University Dental School, Chicago

DENTAL CARIES—ITS CAUSES, CONTROL AND PREVENTION

MAURY MASSLER, D.D.S., M.S.
University of Illinois College of Medicine, Chicago

Presented at the Annual Meeting of the American Academy of Pediatrics, Chicago, Oct. 17, 1951.

INTRODUCTION TO ORAL HEALTH IN PEDIATRICS

JOHN A. BIGLER, M.D.

Symposia on oral health in children have been all too few on pediatric programs. Although there have been numerous articles in the dental and public health journals, comparatively few have appeared in pediatric and other medical literature. When one considers that children are particularly vulnerable to dental caries and it is estimated that 92% of the population have some dental problems, the importance of this subject becomes evident.

There are not enough dentists in this country to take care of the problems. For this reason, prevention and control of dental caries becomes the responsibility of the physician as well as the dentist. It becomes even more an obligation than a responsibility because we as pediatricians assume care that makes for total child health.

With this in mind the pediatrician must keep abreast of the theories of dental caries initiation, its control and prevention. He should also recognize when children are getting proper dental care.

THE RESPONSIBILITY OF THE PEDIATRICIAN IN RELATIONSHIP TO ORAL HEALTH IN PEDIATRICS

ARTHUR F. ANDERSON, M.D.

The dento-facial apparatus is one of the important organs of the body. It contributes much to the appearance and personality of the individual. Its primary function, however, is the procurement and early preparation of food.

Dysfunction of the organ frequently results in dysfunction of the digestive tract. Accordingly, reappraisal of its physiology and pathology seems imperative.

Disorders of the dento-facial apparatus frequently are present at birth. They usually interfere with nursing. Dento-facial dysfunctions are also responsible in many infants for faulty chewing habits during the latter part of infancy and early childhood.

In later childhood, dysfunction caused by maloccusion may result in early periodontal disease. In adolescence, it may incite serious psychologic disturbances.

Dental caries is one of the most universal and crippling diseases. Treatment, once the disease has been established, is far beyond the powers of the dental profession. Prevention alone offers hope of controlling it. Fortunately, recent advances have greatly enhanced such hopes.

Heretofore pediatric curriculae have woefully neglected this very important subject. Where already instituted, instruction in pediatric dentistry has found favor with the students and internes and should be adopted generally.

DENTAL DISEASE AND ITS EFFECT ON THE ORAL MECHANISM OF THE CHILD

J. R. BLAYNEY, D.D.S.

The human denture must be considered as a single unit composed of several component structures, like all other organs. Too frequently the individual tooth is thought to be the unit.

Teeth are dynamic and not static as often considered. Disease, or the loss of an individual tooth, is likely to seriously disturb the function of the entire denture which will lead to the development of other pathologic processes.

The most important dental disease of the child—dental caries—may be controlled by the utilization of our present knowledge. The pediatrician has an important responsibility in the preservation of the health of the oral cavity. Prevention of this phase of dental disease can be accomplished only during the childhood period.

MALOCCLUSION—ITS EFFECT ON THE ORAL MECHANISM

JOHN R. THOMPSON, D.D.S.

The scope of orthodontics has been broadened to include the maintenance of as near normal function and appearance of the entire masticating system of the individual as is possible. The system

includes not only the teeth and their direct supporting tissues but also the mandible and maxilla proper, the temporomandibular articulations, the musculature with its nerve and vascular supply and other less important but nevertheless necessary structures. The parts of the system must never be thought of as individual units but always collectively with the realization that detrimental changes in one part will have their influence similarly on the others and on their coordinated function.

It is becoming apparent that most malocclusions are morphologic rather than metabolic in nature. For this reason a program of prevention will not solve the problem of "orthodontics for the masses."

The introduction of cephalometric radiography that permits serial as well as singular accurate evaluation of the facial skeletal pattern of the prospective orthodontic patient has given us a better understanding of the problem at hand. Diagnosis can now be made on a basis other than conjecture. Methods and age of instituting treatment are undergoing alteration.

MANAGEMENT OF PROBLEMS RELATING TO THE DENTAL CARE OF THE CHILD

GEORGE W. TEUSCHER, D.D.S.

The practice of pedodontics deals with several problems which are different to a great extent from those confronted in practicing dentistry for adults. The psychologic problems are different and require a thorough knowledge of growth and development if they are to be properly managed.

It is difficult to convince children that there are certain diet rules to which they must adhere if the teeth are to be kept in good condition. Many of them fail to grasp the importance of maintaining mouth cleanliness. Couple these 2 things, and irreparable damage may result to the teeth and soft tissues. Too frequently, parents fail to realize these things and give no guidance to the child in establishing and maintaining proper oral health; so, there is a constant job of education to be performed.

Prevention of oral disease should play a major role in a pedodontic practice. It is with children that we have the greatest opportunity for prevention. The large majority of children start life with healthy mouths. The greatest achievement in dental practice is to keep them that way.

Other common clinical conditions and problems will be discussed briefly. The role of anesthesia will be discussed and some of the more common mouth infections considered.

DENTAL CARIES—ITS CAUSES, CONTROL AND PREVENTION

MAURY MASSLER, D.D.S., M.S.

Greater progress towards the control and prevention of dental decay has been made in the last decade than during the preceding centuries. Several methods have been proposed. All are undergoing careful scientific testing and critical clinical scrutiny. Three procedures (sugar control, fluoride therapy and ammonia-urea compounds) show definite promise and, in fact, have already been applied clinically.

Sugar control has been demonstrated to be an effective means of controlling active caries. Sugar control has also been suggested as a preventive measure. Sugar control is in fact the only successful method in the dietary control of caries, all other dietary factors (vitamin D and calcium) having been found to be therapeutically ineffective. However, sugar restriction on a large scale is doomed to failure because of the enormous sugar appetite of the child.

Fluorides hold some promise of providing an effective method of caries prevention on a massive scale (when added to the communal water supply). Ammonia-urea compounds added to dentifrices and mouth washes show promise of inhibiting caries activity. However, the ammonia-urea compounds have not yet received complete clinical testing. More recently, dentifrices containing penicillin have been suggested for the prevention of caries.

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SPECIAL SECTIONS

THE PEDIATRICIAN AND THE PUBLIC

"A forum where discussion could be free, intelligent and continuous"

PAUL A. HARPER, M.D., *Editor*

Statements appearing in this column do not necessarily reflect the opinion of the editor nor are they to be interpreted as the official opinion of the Academy.

COMMUNICATION FROM DR. T. CAMPBELL GOODWIN

THE following communication describes an attempt to provide a rural community with the type of medical services which are ordinarily to be found only in medical centers. This is a two-way program which recognizes that experience in rural practice is valuable for the training of medical students, house officers and nurses. The author, Dr. T. Campbell Goodwin, was engaged in the private practice of pediatrics in Baltimore and was a pediatrician at The Johns Hopkins Hospital prior to joining the staff of the Mary Imogene Bassett Hospital at Cooperstown, N.Y.

DEAR DR. HARPER:

While visiting here last summer Dr. Edwards A. Park suggested that the experience in group practice at the Mary Imogene Bassett Hospital might be of interest to the readers of your column. It would be well to give a brief description of the geography and demography of the surrounding region.

Cooperstown, about 20 miles from the nearest railroad passenger station with a population of three thousand, is the county seat of Otsego in Eastern Central New York State. It is twelve hundred feet above sea level in the foothills of the Catskill Mountains and has been settled since the end of the eighteenth century. Agriculture and dairy farming are the chief means of livelihood of the country folk, while in the towns, stores and occasional small manufacturing plants provide a living for others. One-third the county population is urban, one-third farming and one-third rural non-farming. In Cooperstown itself the National Baseball Hall of Fame, the New York State Historical Museum and the Farmers' Museum bring over two hundred thousand visitors each year. Some of these use our hospital facilities. The staffs of the museums, the nearby educational institutions, retired professional people and summer visitors make up another group of people among whom

we practice. The county of Otsego has the oldest average age group of any county in New York State. Most of the population is economically self-supporting, politically conservative and varied in national and religious background. Comparatively few in the area are wealthy and few destitute, although nearly half of the county budget is spent on welfare. The civic generosity of some of the more wealthy residents was, unfortunately, followed for many years by the all too easy attitude of laissez faire. That together with the conservatism of an isolated group has made for slow change. Thus the progress achieved has been real proof of the idealism, determination and persistence of those who saw it through.

Mary Imogene Bassett, the daughter of two local physicians, practiced medicine in Cooperstown. During the second decade of this century she was the beloved dean of practioners in the region. It was through the generosity of one of her patients, Edward Severin Clark, that the hospital bearing her name was built in 1918. For its first two years it was used by the Government as a convalescent home for airmen. Four years later it was opened to the public with Dr. Bassett as Chief of a staff made up of the local physicians. Her death the same year was followed by an unfortunate period of differences of opinion among the various members of the professional staff and the trustees as to the function of the hospital. In 1925, the well-equipped hundred bed building closed its doors.

With additional financial backing and somewhat broader objectives the hospital reopened in 1927. Physicians with special training and academic background were brought in on a full time basis to head the various departments. The policies, confused at first, finally clarified under the leadership of Dr. George M. Mackenzie, who for nearly two decades ably directed the institution. The aim was to bring to a rural community a general hospital with the atmosphere and opportunities of the better teaching hospitals. The policies as Dr. Mackenzie stated in 1942 were shaped by the following concepts. "1). Careful planning and constant efforts to maintain conditions of work which will promote professional growth, 2). Replacement of extreme professional individualism by collective enterprise, 3). Elimination as completely as possible of the private enterprise quality, and the private profit motivation of the doctor-patient relationship, 4). Provision of funds and of opportunities for clinical investigation and research in medical sciences, and 5). An appreciation of the social significance of disease."

All the doctors in the community were invited to join the hospital staff on a full time salaried basis and all but one did so. As these older practitioners retired or died, younger physicians with academic background and thorough training in their specialty were added to the staff. At the present time there is only one physician in the community not on the staff of the hospital. With the growth of the hospital there have been established departments of medicine, surgery, obstetrics and gynecology, pediatrics, radiology, otolaryngology, pathology and clinical laboratory. There are, in addition, consultants in ophthalmology and dentistry and future plans include departments in these specialties as well as in psychiatry and orthopedics.

The desirability of an official academic connection for this hospital was obvious. For many years the post-graduate training of interns and residents has been accepted, and 15 years ago undergraduates began to come to the hospital for training during their elective periods. Most of them came from the College of Physicians and Surgeons in New York City. Their enthusiasm and the demonstration that the rural hospital could provide a valuable experience not otherwise available in the curriculum led to a formal affiliation

with Columbia University. Fourth year medical students in groups of five are sent to Cooperstown throughout the year to act as junior interns for two months at a time. They live in the hospital, take part in the various exercises and have an opportunity to observe and participate in the practice of medicine in a rural community. Senior members of the staff have appointments on the teaching staff of the College of Physicians and Surgeons.

In the beginning it was not easy to convince conservative upstate New Yorkers of the value of this new type of medicine. Personal jealousies and suspicion helped to delay the general acceptance of the hospital and its staff as the "family physician" for the community. However, over the years there has been a steady increase in the number of patient days, the percentage of babies of the community born in the hospital, and the number of clinic and domiciliary visits. Gratifying, too, is the sharp rise in the past few years of the number of patients sent to the clinic for consultation by physicians in neighboring counties. The attitude in the community at the present time is one of confidence in the hospital and pride in its accomplishments.

This county has as yet no completely organized public health unit with its various services. Some years ago a County Laboratory was established in the Mary Imogene Bassett Hospital and it still functions actively as an adjunct to the hospital laboratory. The hospital pathologist is the Director of the County Laboratory. Both the local Public Health Officer and the School Physician are members of the hospital staff. Through these three links the hospital maintains a close connection with the problems of community public health.

For a period of nearly 10 years an experiment in prepaid medical care was conducted in Cooperstown. For fees ranging from $25 for an individual and $100 for a family, medical care was provided. This included all hospitalization, surgery, professional fees, home and office calls and preventive procedures. It did not include obstetrical care. From the point of view of the hospital the experience was successful. If one may judge by a steadily increasing community participation, and the large number of annual re-enrollments, the community also approved the plan. At the urgent request of the New York Council of Social Agencies, who were currently backing the newly formed Blue Cross insurance in this area, the annual prepayment plan was discontinued in 1940. The plan brought good medical care to many individuals at a very low cost. Since its proceeds provided only about half of the running expenses of the hospital there was a real question of its financial soundness. It was thought then that more money came to the hospital from the annual payments than would have been collected from bills sent the patients for the same service rendered on an individual charge basis. The operating deficit of this hospital has been large, averaging more than 50% of the operating expenses through the year 1946. This deficit is made up from the funds turned over to the hospital by the Clark and Scriven Foundations as a permanent endowment. The proceeds of this fund enable the hospital to keep the ward rates for patients at a figure that will be covered for those participating in the Blue Cross and Blue Shield programs.

The difficulty in obtaining an adequate number of nurses in rural areas has always been a serious problem. A year ago an affiliation was made between Bassett Hospital, Hartwick College of Oneonta, 20 miles from Cooperstown, and the Nursing School of the Columbia-Presbyterian Medical Center in New York. Girls from this region are given a full nursing course in these three institutions leading to a college degree. There is an emphasis on the training given in public health nursing, particularly as related to rural problems. It is hoped that many of these young women will return to practice their pro-

fession near their homes, and thus solve in some measure the local problem of a nursing shortage.

Pediatrics was begun in this region as a specialty when, in 1929, Dr. Marjorie Murray came to Cooperstown as Chief Pediatrician of the Bassett Hospital. In a few years through her love of people, untiring industry and sound judgment this specialty was well established as an integral part of medicine in the community. She and her associates developed in the local people an appreciation of the importance of immunization procedures, clean and proper diets and of the role of emotional problems in the development of their children. It has been both interesting and gratifying to see the principles and practice of sound pediatrics spread not only in the immediate environs of the hospital but by the education of doctors and parents to communities many miles away. The small size of the in-patient pediatric service, 15 beds, has made possible more individualized patient care than is practiced in most of the larger children's hospitals. The encouragement of parents staying with the children in the hospital and working with the staff to solve the emotional, feeding and adjustment problems of the sick child has in our opinion speeded recovery and aided convalescence. We feel that this is as important in the care of the sick child as the principles of rooming-in are to the care of the newborn.

The close cooperative connection between the hospital and local schools has made possible the establishment of an adequate system of physical examination of all school children during the first week of the fall session. This gives more opportunity for the follow-up of children with recognized defects during the remainder of the year. This cooperation also has made possible almost total participation in programs of immunization, tuberculosis case finding, follow-up clinics for the hard of hearing and now various phases of mental health. People of the community have become cognizant of and educated to the advantages of having a child seen in the clinic rather than at home. Last year only 6% of the pediatric patient visits were at home.

When one thinks of the advantages of medical practice in such a clinic as the Bassett Hospital, economy of time is high on the list. The centralization of office, clinic, ward, library and laboratory under one roof eliminates many useless hours of transit. The easy availability of the laboratories, hospital and community enables the members of the staff to combine some type of investigative work with a full clinical program. The willingness of the patients to come to the clinic enables us to use the laboratory and other hospital facilities to give the patient a much more complete and satisfactory examination than usually can be accomplished in the office of a rural physician. The easy availability of consultants plays a large part in bringing better medical care to the community. The atmosphere of teaching and medical growth is reflected in the more accurate diagnosis and better care of patients. The staff rounds and other formal teaching exercises are, of course, open to any doctors who wish to attend, and the physicians in the area are specifically invited. The response to this phase of the education program has been disappointing.

Perhaps it would be just as well now to discuss some of the disadvantages and drawbacks of this type of group practice. The disadvantages to the physician are those resulting from living in a small social and medical community, and at the same time attempting to maintain professional growth, and the ability to teach intelligently and enthusiastically. The obvious answer to this problem is for the members of the staff to get away periodically for study and discussion. This attitude is fostered by the institution.

The disadvantages to the patient are, perhaps, more difficult to define and are often

minimized by those with a more academic viewpoint. The desire of a patient or a family to have a family physician has grown up through countless generations. With the present age of specialization and the increasing importance of laboratory procedures in the care of the sick some of this feeling has broken down. But many times even the specialist has assumed the role of confident and family adviser. This is especially true of the obstetrician and pediatrician. When an institution with a changing staff takes on the role of family physician many times it is impossible for a patient to have the same physician for each visit or illness which may lead to expressed or implied dissatisfaction. By careful management and planning this objection to group practice can be minimized but not eliminated. It by no means offsets the advantages of better medical care enjoyed by most of the community, but will to certain individuals mean a less desirable type of medical care, which holds until one or perhaps many new generations have grown up.

This brief description touches only a few of the problems we have faced, and, perhaps partially solved, in the practice of medicine in a rural area. A wide vista or problems for investigation in rural sociology, the practice and economics of rural medicine, epidemiology and countless other fields are a constant challenge. We would like to feel that the experiences at the Bassett Hospital during the past generation will be of help in the solution of similar problems elsewhere. I am appending a short bibliography which may be of service to those who would like a more detailed discussion of the topics I have mentioned.

T. CAMPBELL GOODWIN, M.D., *Cooperstown, N.Y.*

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TRENDS

By JOHN P. HUBBARD, M.D., *Contributing Editor*

This and subsequent descriptions of events and trends are intended to be unbiased and factual, presenting both sides of controversial matters so that conclusions may be formed from critical appraisal of things as they are. These statements do not necessarily reflect the opinion of the writer nor are they to be interpreted as official opinion of the Academy.

EMIC AGAIN?

IS THERE to be another EMIC program? This question is heard again in Washington, in various state health departments, in gatherings of interested persons, and among those physicians primarily concerned: pediatricians, obstetricians and general practitioners.

It is not our purpose to argue for or against an EMIC rebirth, but rather to report the status of the proposals which have already appeared, bearing in mind that the scene may have shifted much or little between the present date (May 28) and the appearance of this column.

As the tempo of the Korean War and war mobilization increased during the early months of this year, it was hardly surprising that consideration should again be given to medical care for the wives and infants of service men. In February there were informal discussions between the Children's Bureau staff and the AMA. In early March, the Committee on Maternal and Child Care of the AMA Council on Medical Services met and discussed the possibility of revival of EMIC. Those attending this meeting included Dr. Lull and others from the AMA, Miss Lenroot, Dr. Blain and Dr. Daley from the Children's Bureau and Drs. Barba, Webb and Christopherson from the Academy. A questionnaire to elicit comments on the EMIC had been sent out to District and State Chairmen of the Academy, to all State Medical Societies, to individual pediatricians and obstetricians and to others who had been vocal about the old EMIC. In the general discussion it was brought out that the Child Welfare Committee of the American Legion had passed a resolution, which was adopted by the Assembly, recommending a revival of EMIC with modifications to avoid the former difficulties and objections.

Also in early March, when the Executive Committee of the Association of State and Territorial Health Officers met with the Children's Bureau in Washington, the Committee determined at that time that there was not sufficient evidence of need to justify the support, promotion or introduction of legislation for this purpose. However, it was thought advisable, because of the difficulties and strained relations incurred by EMIC during World War II, to review the policies and procedures of administration which would be required in such a program if legislation of this nature were to be introduced. Thus, by planning ahead, it was hoped to avoid many of the former irritations which came from hasty arrangements.

On March 20, Representative Flood of Pennsylvania introduced H.R. 3349 which proposes a program quite different from that in effect during World War II. This bill provides that the wife of any member of the Armed Forces should be allowed $100 for the expenses incurred in childbirth, if such expenses are found to constitute an undue financial hardship. The old EMIC was administered by the Children's Bureau; according

to the Flood bill payments would be made by the Secretary of the service in which the husband is serving. Formerly, a flat fee not to exceed $50 was paid to physicians for expenses of childbirth, including delivery, prenatal and postnatal care, and the payment of hospital expenses; here an amount of $100 is proposed, payable directly to the wife of the service man.

On April 2, Senator Humphrey of Minnesota introduced S. 1245 which would establish a program similar to the plan in existence during World War II. The Children's Bureau would be authorized to make grants to states in accordance with the financial need of each state, as determined by the administrator. This bill does not attempt to establish fees for physicians or rates of payment to hospitals, such matters being left to the judgement of the administrator in the writing of regulations. In the Humphrey bill it is proposed that the wives and children of all enlisted members of the Armed Forces would be eligible to receive benefits, whereas the old EMIC plan gave benefits only to the dependents of enlisted personnel in the lowest four pay-grades.

At the state level, at least one state has gone on record for an EMIC program. At the time Senator Humphrey introduced S. 1245, his fellow Minnesotan, Senator Thye, filed a joint resolution of his state legislature requesting "immediate" enactment of EMIC legislation to relieve "suffering and hardship (that) has been experienced by pregnant wives . . . owing to the absence of their husbands from home."

On April 4, a special conference was called by the Children's Bureau for the purpose of discussing ideas as to how EMIC should be developed if pressure for it gathers momentum. This meeting was attended by representatives of the AMA and the Academy and included also others from the ranks of the pediatricians and obstetricians. One of the suggestions which arose from this conference was that the medical profession have a more prominent role in the administration of the plan than existed under the old EMIC. The Children's Bureau concurred in this suggestion, stating: "It was recognized that advisory consultation with medical and hospital groups would be particularly important."

The present attitude of the AMA is reported in a Bulletin dated May 1, 1951, from the Washington office which states "At its most recent meeting, A.M.A.'s Board of Trustees and Legislative Committee voted to oppose both bills (H.R. 3349 and S. 1245), a major contention being that they are not necessary at this time. In commenting upon the attitude of the A.M.A. Committee on Maternal and Child Care, Dr. Lull, in his Secretary's Letter of April 30, states that "Committee Chairman W. L. Crawford says he believes the evidence at hand so far indicates that no wide spread emergency exists at the present time for setting up a special maternal and infant care program for wives and dependents of service men. He adds that as nearly as the committee can determine, there have been only a few requests or pressures for a nationwide reenactment of such a program. The few requests that have been received usually can be traced to individual instances arising near military installations where the influx of service men and their families has resulted in abnormal conditions. Special considerations and planning, Dr. Crawford believes, will have to be given to these particular areas."

According to present planning, hearings on the EMIC bills are scheduled for some time in June. As to their chances of favorable action, one sage observer of the Washington scene, Mr. Gerald Gross, indicates in his *Washington Report on the Medical Sciences,* April 30, 1951, that EMIC stands the best chance among the pending bills for health legislation. "At this stage," he states, "congressional approval of a new model EMIC plan continues to have a bullish outlook, notwithstanding low estate of other

health bills of national significance. Covering as it would only the wives and infants of men in uniform, this legislation when whipped satisfactorily into shape may be expected to be justified and passed as an essential cog in strengthening and development of the military services."

A more recent development was the introduction into the House of a bill (H.R. 4176), identical to the Senate bill (S. 1245). This House bill was introduced by Representative Mitchell on May 21. An interesting note was the fact that it was not referred to the House Interstate and Foreign Commerce Committee, to which health bills are generally referred, but it was sent to the Armed Services Committee. This action links the measure more directly with the needs of the Armed Services and may indicate speedier action.

NEWS AND ANNOUNCEMENTS

The following officers were elected to the American Pediatric Society at the Annual Meeting held in Atlantic City, May 3, 1951:

President—Dr. Hugh McCulloch
Vice President—Dr. Arthur H. Parmelee
Secretary-Treasurer—Dr. Aims C. McGuinness
Editor and Recorder—Dr. Stewart H. Clifford

Dr. Hattie E. Alexander was elected to the Council for a 7 year period. The following candidates were elected to active membership in the Society:

Sidney S. Chipman, Chapel Hill, N.C.
Leonard T. Davidson, Louisville
Harry F. Dietrich, Los Angeles
Edith B. Jackson, New Haven, Conn.
Benjamin M. Kagan, Chicago
Ann G. Kuttner, New York City
Robert A. Lyon, Cincinnati
Machyn McCarty, New York City
Angus McBride, Durham, N.C.
Mila Pierce, Chicago
James G. Hughes, Memphis
May G. Wilson, New York City
Herbert A. Wenner, New Haven, Conn.
Stuart S. Stevenson, Pittsburgh

* * *

Dr. Ji-toong Ling of Norfolk, Va., has been awarded the Fellowship in Pediatric Roentgenology in the Children's Hospital of Cincinnati. He will begin his studies July 1, 1951.

* * *

Dr. Byron K. Rust of Indianapolis has been appointed to the National Medical Advisory Board of the American Legion.

* * *

A training course in the diagnosis and treatment of epilepsy, and in electroencephalography is to be conducted at the Seizure Division of the Children's Medical Center in Boston, under a special grant from the Children's Bureau, acting through the Massachusetts Department of Public Health. A limited number of physicians and prospective electroencephalographic technicians will be accepted. The first course begins July 1, 1951. Details may be secured from state or territorial health departments, or from the Children's Medical Center, 300 Longwood Avenue, Boston.

* * *

Pediatric Post-Graduate Endocrinology Course at the Burnham Memorial Hospital for Children, Massachusetts General Hospital, Boston, Oct. 1 through Oct. 6, 1951, daily 9:00 a.m. to 4:30 p.m.

For further details write Courses for Graduates, Harvard Medical School, 25 Shattuck St., Boston.

* * *

M & R PEDIATRIC RESEARCH CONFERENCES

During the past winter the McKesson & Robbins Laboratories have established the M & R Research Conferences. The primary purpose of each conference is to facilitate the exchange of information between active investigators in particular fields of pediatric research.

The first conference was held Nov. 16, 1950, in the Burnham Memorial Hospital for Children at the Massachusetts General Hospital under the chairmanship of Dr. Allan M. Butler. The subject was the role of B-12, Folic Acid, Cirtrovorum Factor and Vitamin C in the megaloblastic anemias of infancy.

The second conference, held on April 28, 1951, at New York University under the chairmanship of Dr. L. Emmett Holt, Jr., dealt with the Etiology and Therapy of Retrolental Fibroplasia.

It is anticipated that conferences on various subjects will be held annually.

The following diplomates were certified by the American Board of Pediatrics, Inc.:

Atlantic City—May 5, 6 and 7, 1951

Aisenson, Milton R., 144-16 72nd Ave., Flushing, N.Y.
Barol, Daniel H., 1811 Pine St., Philadelphia
Barrett, John Telfer, 122 Waterman St., Providence, R.I.
Beaven, Charles William, 87 29th St., Newport News, Va.
Bleiweiss, Irwin M., 1855 Grand Concourse, Bronx, N.Y.
Cardany, George J., 7104 Chatham Rd., Chevy Chase, Md.
Chiara, Nicholas H., 7200 Ridge Blvd., Brooklyn
Cohn, Perry David, 231 Lexington Ave., Passaic, N.J.
Cote, Marie Leonore, 273 Liberty St., Newburgh, N.Y.
Diamond, Jess, 840 Grand Concourse, New York City
dos Remedios, Leonardo Vincente, Dept. of Pediatrics, New York Hospital, New York City
Eckhardt, George Conrad, Streptococcal Disease Laboratory, Warren Air Force Base, Cheyenne, Wyo.
Elson, George Y., 1801 Olney Ave., Philadelphia
Filsinger, Carl William, 109 W. Maple Ave., Merchantville, N.J.
Friedman, Sidney, 1740 Bainbridge St., Philadelphia
Gelfand, Daniel E., 1575 Krameria St., Denver
Grayson, Robert, 612 71st St., Miami Beach, Fla.
Heimer, Caryl Biren, 105 Lincoln Rd., Brooklyn
Johnson, James Franklin, Dept. of Pediatrics, New York Hospital, 525 E. 68th St., New York City
Johnstone, Douglas Edward, Baltimore City Hospitals, 4940 Eastern Ave., Baltimore
Kaye, Robert, Children's Hospital of Philadelphia, 1740 Bainbridge St., Philadelphia
Kornfeld, Werner, 135 S. Munn Ave., East Orange, N.J.
Lambert, Edward Cary, 459 Berrymen Drive, Snyder, N.Y.
Lenihan, Thomas Francis Xavier, 2503 Fairlawn Ave., Fairlawn, N.J.
Levitzky, Edward, 1130 Jefferson Ave., Rahway, N.J.
Mancusi-Ungaro, Harold Raymond, 480 Grove St., Upper Montclair, N.J.
Margolis, Bernard, 5102 Diamond St., Philadelphia
Milan, Enrique, Santa Ana 18, Ocean Park, Santurce, P.R.
Miller, Bertram Wilson, 169-02 32nd Ave., Flushing, N.Y.
Morgan, William Clayton, Professional Bldg., Salisbury, Md.
Murphy, Mary Lois, Camden Municipal Hospital, Camden, N.J.
Narrett, Sidney S., 140 Passaic Ave., Passaic, N.J.
Nightingale, Janice Tulchin, 545 E. 14th St., New York City
Nitchman, Donald E., 174 Sunnyside Rd., Scotia, N.Y.
Pomerance, Herbert Hart, 69-49 173rd St. (Utopia Station), Flushing, N.Y.
Prystowsky, Milton, Harriet Lane Home, Johns Hopkins Hospital, Baltimore
Randolph, Martin Francis, 345 Main St., Danbury, Conn.
Robbins, Frederick C., 300 Longwood Ave., Boston
Roberts, Dudley Albert, 124 St. Paul St., Westfield, N.J.
Saigh, Raymond, 174 Ivy Lane, Teaneck, N.J.
Schneider, Milton, 213-03 35th Ave., Bayside, N.Y.
Schwartz, Ralph, 2017 Grand Concourse, New York City
Shapiro, Allen David, 202 Grand St., Newburgh, N.Y.
Shelley, John Howland, 91-10 158th Ave., Howard Beach, N.Y.
Shuman, Bernard J., 2643 Pacific Ave., Atlantic City
Soifer, Hyman, 105-05 69th Ave., Forest Hills, Queens, N.Y.
Stengel, William Frederick, Johns Hopkins Hospital, Baltimore
Stiles, David, 14 S. Broadway, Irvington-on-Hudson, N.Y.
Tisza, Veronica Elizabeth B., 44 Bowdoin St., Cambridge, Mass.
Wallace, Edward Paez, 78 Federal St., Greenfield, Mass.
Ward, Richard Storer, 44 W. 12th St., New York City
Weinstock, Jerome Leonard, 5346 Gainor Rd., Philadelphia
Welner, Daniel Harris, 673 Parkside Ave., Buffalo, N.Y.
Wendell, Kathleen Kirk, 758 High St., Pottstown, Pa.

The twenty-first meeting of the Society for Pediatric Research was held on May 2 and 3, 1951, at the Hotel Traymore in Atlantic City. The following officers were elected:

President: Horace L. Hodes, New York City
Vice President: Harold Wright
Secretary-Treasurer: Sydney S. Gellis
Members of the Council: Edward L. Pratt
Nelson K. Ordway
Charles D. May

The following candidates were elected to membership:

Lewis Barness, Philadelphia
Alfred M. Bongiovanni, Philadelphia
Henry B. Bruyn, San Francisco
Phillip L. Calcagno, Buffalo
Robert E. Cooke, New Haven
John D. Crawford, Boston
Lytt L. Gardner, Chapel Hill
Robert Good, Minneapolis
Ruth G. Harris, New York City
Andrew H. Hunt, Philadelphia
Vincent C. Kelley, Minneapolis
Robert Klein, Baltimore
Jonathan T. Lanman, New York City
Bruce Mackler, Cincinnati
Marion Maresh, Denver
Wallace W. McCrory, Philadelphia
Paul R. Patterson, Boston
Victor C. Vaughan, III, New Haven
Dwain N. Walcher, Indianapolis
Thomas H. Weller, Boston
Calvin W. Woodruff, Nashville

BOOK REVIEWS

SOME PROBLEMS OF CHILDREN, Wendell Johnson, New York, Grune & Stratton, 1950, $3.75, 265 pp.

This volume was prepared for the National Society for Crippled Children and Adults by The American Speech and Hearing Association. Its 11 chapters were written by assigned authors and then reviewed and criticized by professional consultants before the final editorial work by the editor. In this way as much agreement as possible was obtained among the speech pathologists involved. The book is described as "an attempt to produce a dependable book of interest to parents, teachers, social workers, physicians and others who are not professional speech correctionists but who are nevertheless concerned, of necessity, with the speech handicapped." It is written in a simple straightforward style which is easy to follow and remarkably free from technical jargon. A general mental health orientation is found throughout. There is indicated a high respect for the individualness of each child and the individualistic nature of growth patterns. By and large it is not threatening to parents and it should not contribute to the anxieties of parents as do so many publications. In fact, it should be reassuring; there are so many simple practical and direct things pointed out for them to do. There is a stress on the positive with, on the whole, a minimum of negative advice.

There are chapters on speech in the home and in the school. Other chapters deal with broad categories of problems, children who "don't talk plain," who are slow in learning speech with cleft palate and cleft lip, with cerebral palsy, with voice disorders, with hesitant speech, with foreign tongues and with impaired hearing. Stuttering is gone over lightly in the chapter on hesitant speech; this is apparently deliberate.

On the whole the book does nicely what it set out to do. Intelligent, well integrated parents can get a lot out of it that is helpful. General physicians can also find it useful as a survey of the speech problems which can be approached through speech training and general application of mental hygiene principles. Teachers, too, may from reading this develop a greater tolerance for children with speech disorders. The speech disturbances which are a part of well marked personality disorders are not discussed adequately; these of course need a general psychotherapeutic approach primarily.

On page 127 there is, in connection with the discussion of children with cleft palate and cleft lip, a strong plea made for the prevention of respiratory infection. The way this is written is quite apt to produce over-concern and resultant over-solicitousness in the parent. Sure-fire methods of preventing respiratory infections are still not a reality.

PROGRESS IN CLINICAL ENDOCRINOLOGY, Samuel Soskin, M.D., New York, Grune & Stratton, 1950, $10.00, 641 pp.

This is the first volume of an intended series of periodically published, single volume, critical reviews indicating the progress of clinical endocrinology. The editor is Director of the Medical Research Institute of Michael Reese Hospital in Chicago. For this purpose, he has gathered for this initial volume 79 articles by an almost equal number of authors—each dealing with a different phase of the subject. The articles are short, readable, and to the point, averaging 7 pages in length. While essentially practical in their approach, the various authors give adequate emphasis to experimental and theoretic background material, and a comprehensive, up-to-date bibliography accompanies each article.

Considerable care is shown in achieving a broad and authoritative coverage of an admittedly large and confusing field. This volume will be of considerable interest and assistance to any pediatrician, internist, surgeon or general practitioner who accepts patients with endocrine problems, and is recommended by the reviewer as an excellent supplement to textbooks.

THE ENVELOPE, James S. Plant, M.D., Sc.D., New York, Commonwealth Fund, 1950, $3.00, 299 pp.

The author of this book is well known to American pediatrics because of his writings on behavior and child psychiatry. Up until his death in 1947, he was for 24 years Director of the Essex County Juvenile Clinic in Newark, N.J.

The author was interested in psycho-social as well as psychobiologic and psychosomatic aspects of life and this interest is carried forward in the present book. It is in a way a continuation of an earlier book titled *Personality and the Cultural Pattern,* which had wide acceptance among the medical and social sciences.

The title of the book is taken from the author's thesis that each human being has a personality which is covered with a sort of psycho-osmotic envelope "of transcending importance between the need of the child and the sweep of social pressures." The envelope is an intangible something but a distinct property of the personality, through which it is in touch with the environment. The envelope in theory is able to shut out or take in, and use sectors of the environment, and the author likens his theory to Freudian psychoanalysis although he was not himself such an analyst. Plant was interested in showing his audience how the envelope acts protectively and how it uses defensive properties.

In this book Plant discusses personality but does not aim to describe it; instead he emphasizes the fact that there are recurring patterns in growth and that the implication of this in terms of total personality development in cultural patterns needs to be understood. This concept has special meaning to the pediatrician. The bulk of the book consists in presenting 21 problems which Plant found were common to most of the children with whom he came in contact in his clinic. These problems include security, authority, status preservation, the feeling of difference, symbolization and reality, physical expression of the sexual urge, temperament, reaction to failure, intelligence, sibling rivalry and several others. Each problem is discussed in a separate chapter but there is a running theme between them. The problems are analyzed in terms of focal periods in the life of each child, for example, birth, period of infant feeding, the time when a sibling is born, the period of starting a school, and adolescence. A sample of the manner in which the author discusses each problem may be taken from the chapter on security. In this part one finds first a definition of security along with reasons why a child is secure or insecure. The status of the child in the family, the member role of his family in the community, sibling rivalry, the degree of belongingness to parents or to their substitutes such as teachers—are all investigated in terms of their importance in fostering security or in denying it to the child.

The author demonstrates his broad interest and background by describing not only psychologic mechanism at work in every child, but also those sociologic and cultural trends which he believes are at work in our society. Throughout is woven his philosophy as a psychiatrist, but in this he is independent of any of the other dominant schools such as the psychoanalytic or the psychobiologic. The book provides a broad background for understanding the behavior of children and should be found of particular value to psychiatrists, psychologists, philosophers and social workers. The pediatrician will find it stimulating and broadening but will be disappointed if he is looking for pat remedies for the many behavior problems which come to him in his everyday practice.

SERUM SICKNESS, Clemens von Pirquet and Bela Schick, translated by Bela Schick, Baltimore, Williams & Wilkins Company, 1951, $3.50, 130 pp.

This is a classic of medical literature, written by 2 young men: at the time of its publication Schick was 28, Pirquet a few years older. We know of no other such which has been translated by one of the authors, nearly 50 years after its original publication. It is a classic because it is a brilliant investigation of basic phenomena of much import to immunology, and because it built the foundation for what Pirquet later called "Allergy."

It is divided into 3 parts: 1. Clinical aspects of serum sickness; 2. The reinjection; 3. Theory of serum sickness.

The first section comprises 60 pages. This is a detailed protocol of painstaking clinical observation: no disease has ever been described with more accuracy or thoroughness.

It is the second part, "The Reinjection," which gives the monograph its place as a fundamental contribution to immunology.

By 1905, diphtheria antitoxin had already been in use for several years, and it was expected as a matter of course that a considerable number of those who received it would develop "serum sickness" 8 to 10 days after its administration. It had also been noted that after a second injection the reaction was likely to be immediate, or accelerated, without the usual incubation time. Little attention was paid to this, until its true significance was recognized by Pirquet and Schick.

"Due to a single injection of horse serum a change takes place in the reaction of the human organism to the reintroduction of the same substance, which obeys a definite law. The serum sickness which usually starts after the first injection after an incubation time of several days, appears within a few hours. *The reinjected individual is hypersensitive.* We possess, therefore, in the immediate or accelerated reactivity, a new criterion for the diagnosis that a patient has formerly had the same disease. This statement is not only valid for serum sickness but, as we shall see, for many other toxic and infectious diseases."

This was allergy, although Pirquet did not use the word until a year later, and defined it as follows: "The vaccinated individual reacts differently to the lymph, the luetic to the syphilitic virus, the tuberculous to tuberculin, and the one injected with serum reacts differently to the serum, than does an individual who has never yet come into contact with the given agent. He is, nevertheless, as yet far from being immune, because of this. All we can say about him is that his capacity to react has been altered. I suggest the word 'allergy' to designate this general concept of altered reactivity."*

The third section of the book, for 25 pages, is devoted to a discussion of the serologic changes in serum sickness, and a theory based on these observed changes is present. This theory is still accepted by many immunologists.

The reviewer, only a few days before he was asked by the editor of PEDIATRICS to review *Die Serumkrankheit,* by entire coincidence had the pleasure of discussing the book with Dr. Schick, who, with characteristic modesty, minimized his own part in its production. Nonetheless, no living medical man is held in higher honor than Bela Schick, and it is a privilege and a pleasure to review one of his most important contributions to medicine.

Serum Sickness should be in the possession of every young medical investigator for complete assimilation: it is one of the best examples of brilliant, accurate and logically expressed medical research in the literature.

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* München. med. Wchnschr. **53**:1457, 1906.

THE HANDICAPPED CHILD, Edith M. Stern and Elsa Castendyck, New York, A. A. Wyn, Inc., 1950, $2.00, 179 pp.

Despite the best efforts of the medical profession, there continue to be parents whose children are handicapped either in their senses or in their limbs. For these parents, devoid as they often are of the joy of seeing their child growing up normally, and plagued as they are by both fears and guilt, Mrs. Stern and Miss Castendyck have written this book. As they themselves point out, it is neither a general manual on child care nor encyclopedic in terms of illnesses, but it stresses "the fact that good principles of child rearing apply equally to the normal and the handicapped."

With an extremely frank survey of the feelings of the parents and an appreciation of what the handicapped child means to them, the authors have tried to relieve the unnecessary guilt of parents who frequently feel themselves at fault. Very sensibly they point out the effects of this guilt, either in smothering the child with attention, or being overly demanding. But they also bring out well how human and ordinary it is to become fed-up or overwhelmed with the situation of having a handicapped child. Finally they point out the routes that parents can take to get help both for themselves and for the child.

Following this general statement, the book is divided up by conditions, covering crippled children, as well as children with cerebral palsy, epilepsy and those with impaired sight, vision, and mentality. There is a final chapter on chronic illness, particularly rheumatic fever. Each of these chapters provides concrete advice about the particular condition and offers valuable suggestions as to where the parents may turn. It should not be inferred that the book merely consoles or attempts to minimize the parents' feelings or the child's handicap. It tries to make more clear the crippling aspects of the handicapped, both physically and emotionally, and to help parents clarify their feelings about the child as they work to help him.

While it is obviously impossible to solve all the problems faced by parents whose children are different from others, this book, stressing as it does the underlying principles of good child care, can be of real assistance and support.

YOUR DEAF CHILD, Helmer R. Mykelbust, Springfield, Ill., Charles C Thomas, Publisher, 1950, $2.50, 132 pp.

This is a book written for parents of deaf or hard-of-hearing children. The author is a clinical psychologist whose entire career has been in the field of the education and the psychologic testing of children with impaired hearing. He discusses many of the special problems arising in the rearing of a child with a hearing loss, and gives a good deal of sound advice on a variety of subjects: importance of parental attitudes in child training, discipline, speech training, vocational selection, etc. The approach is necessarily broad, and many parents will find that their specific questions are not answered. There will be few, however, who will not find much of real help.

It would be unwise, however, for pediatricians to recommend this book indiscriminately to parents of deaf children without being aware of some of the book's defects. The most serious of these is the over-simplification in the interests of trying to reach all the book's intended audience, and the constant "writing down" to the less informed portion of that audience. Many parents will resent what they regard as a patronizing air on the part of the author. They will wonder why the author chose to include the childish and irrelevant illustrations.

There are, inevitably, statements which one might question: "All children are especially active before they learn to talk" (p. 42). There are explanations which tell nothing: "Some deaf children learn speech more readily than others because it is easier for them to do so" (p. 76). But the book's virtues are more numerous than its faults, and most parents of deaf children will be grateful to the author.

THE DIAGNOSIS AND TREATMENT OF ENDOCRINE DISORDERS IN CHILDHOOD AND ADOLESCENCE, Lawson Wilkins, M.D., Springfield, Ill., Charles C Thomas, Publisher, 1950, $13.00, 408 pp.

The first 4 chapters of Dr. Wilkins' book are devoted to a general discussion of the endocrine and also the nonendocrine factors influencing growth and development. They present in addition a description of the specialized clinical and laboratory methods used in diagnosis of endocrine disorders. With this background most of the major endocrinopathies are considered in the succeeding chapters. Here the grouping of diseases is made sometimes on the basis of the endocrine system primarily involved, at other times according to an outstanding symptom such as dwarfism or sexual infantilism. The final chapters are concerned with obesity and diseases frequently mistaken for endocrinopathies.

The book is designed to aid the practicing physician in recognizing among his patients those with true endocrine disease. Of particular value in this respect are the numerous illustrations brought together at the end of each chapter and accompanied by legends giving in brief summary the outstanding and distinguishing clinical and laboratory features.

The discussion of ovarian physiology and menstrual disorders seems brief in a book where adolescent endocrine problems are ranked equal in importance with those of childhood. This brevity is in distinct contrast to the relatively lengthy and detailed treatment of adolescence in boys. Diabetes mellitus is not included.

Dr. Wilkins' book is perhaps the first extensive compilation of the primary endocrine diseases of childhood to be published in this country. With it, pediatric endocrinology becomes of age. This book will be an invaluable aid to the pediatric clinician. It will provide a ready source of reference to help him both in recognizing some of the subtle conditions which previously may have escaped his notice and to reorient him concerning some of the nonendocrine disorders which may be mistaken for primary glandular disturbances.

FOOD ALLERGY, Herbert J. Rinkel, M.D., Theron G. Randolph, M.D., and Michael Zeller, M.D., Springfield, Ill., Charles C Thomas, Publisher, 1951, $8.50, 497 pp.

This, in the words of the authors, is a monograph describing the nature and dynamic mechanism of food allergy, and an outline of a practical approach to the problems inherent in its recognition and management.

Food allergy is described as cyclic or fixed. A cyclic food allergy may go through the phases of masked sensitization, omission, hyperacute sensitization, active sensitization, latent sensitization and tolerance. Without a close study of their actual work it is impossible to assess this, but the authors

have positively and accurately described their position in food allergy in such a manner that any debatable points can be readily proved or disproved, and undoubtedly this will be done within a short period. In this way the book performs a most important service in a field where such a service has been needed.

The second part of the book includes the technic of the diagnosis of food allergy. The individual food test is the most important feature. This test must be done with most meticulous care, especially in the complete avoidance of the food during the 4 day period. After frequent use of the food, it is avoided for 4 days. Then a full serving is given, with the patient under careful observation. Under these circumstances if the food is an offender, the symptoms are reproduced. This process is complicated and cannot be explained in a few lines. An escalator diet is also described, which simplifies the completion of the diagnostic work-up. The diets are described in detail and many menus are given.

In this second part of the book, the authors have even more clearly performed a valuable service in standardizing a technic, for the detection of food allergy. It is unlikely that this is the final word on the subject, but the method is so clearly outlined that any fault should be demonstrable.

Statements are made that do not seem to be true. For instance it is stated that "There is a higher average numerical incidence of food sensitivity in adults than in children." It has seemed clear to us that there is much more food allergy among children in the first 3 years of life than among older children and presumably than among adults. Food sensitization is here blamed for many symptoms including flushing, night sweats, chilliness, unexplained fever, fatigue and backache. It is undoubtedly true that some of these symptoms have been due to food allergy, but that this is not a common cause and effect.

The chief criticism of the book is that in their enthusiasm the authors have exaggerated the importance of food allergy in disease, and that some of their assumptions still await confirmation.

TREND DATA FOR THE UNITED STATES, Profile Data for Each State, Federal Security Agency, Children's Bureau, Washington, D.C., 1950.

Some interesting and valuable innovations in presentation are included in this recent Children's Bureau publication which deals with standard indices of concern to pediatricians . . . birth rate, infant mortality rate, preschool and school age mortality rates. One interesting idea is the use of parallel charts showing changes in both an arithmetic scale and a logarithmic scale. Each of these methods has advantages and both are needed to give a full picture of the rates concerned. The arithmetic scale, for example, indicates the comparative importance of a particular cause in any given year and also indicates the absolute size of the rate. The logarithmic scale, on the other hand, is directly adapted for a comparison of the speed of change. For example, if one rate has fallen from 100 to 75 and another from 20 to 15, the arithmetic chart would indicate a large difference in the way the 2 rates had changed because one has fallen 25 lines and the other only 5. On the other hand, the logarithmic chart, designed to show the proportional change, would show similar curves, since the drop in both instances was 25%. An even more striking example is the comparison of one rate which falls from 40 to 30 and another which falls from 10 to 5. The arithmetic chart would show the decline twice as great for the former (10 lines to 5), which the logarithmic chart would show that as regards proportional decline the reverse was true, being twice as great for the latter (50% to 25%).

In addition to trends for the country as a whole, the publication contains, for each state, "profiles" in infant mortality rate, maternal mortality rate, births outside hospitals, and per cent distribution of births by race. Accompanying the details for each state an ingenious graphic device shows the distribution of rates for all the other states in order to make clear the relative standing of the states in which one is interested. The material is clearly presented, easily understood, and will be of great value for those interested in preventive medicine and community planning.

(Copies of this publication may be obtained without charge from the Children's Bureau, Washington, D.C.)

CHEMOTHERAPY OF LEUKEMIA AND LEUKOSARCOMA, William Dameshek, Marvin L. Bloom, Louis Weisfuse, Milton Freedman, and Miguel Layrisse, New York, Grune & Stratton, 1950, $4.75, 53 pp.

In this gratifyingly concise pictorial monograph based on an exhibit prepared for the AMA convention in Atlantic City in June 1949, the authors present the vast data accumulated within the

past decade applicable to the control of leukemia and leukosarcoma. A series of illustrated charts takes the reader rapidly through the difficult procedures of diagnosis so inadequately expressed by any outline, no matter how superbly presented, to the meaty kernel of the monograph, which is a pictorial presentation of the chemical formulas and the physiologic and specific therapeutic effects of various agents in current use. Nitrogen mustard, folic acid antagonists—particularly aminopterin, urethane, radioactive phosphorus and x-ray treatment are presented with indications for the choice of these different agents. Their classification of neoplastic proliferative diseases of white cell tissues defines the leukemias as a generalized, and the leukosarcomas (lymphomas) as the localized, form of these diseases. The classification is subdivided as follows:

Leukemias	Leukosarcomas
1. Myelocytic (Myelogenous) Acute—Subacute—Chronic (Eosinophilic-basophilic types very rare)	1. Myelosarcoma (Chloroma)—Very rare
2. Lymphocytic (Lymphatic) Acute—Subacute—Chronic	2. Lymphosarcoma Lymphoblast Sarcoma Lymphocyte Sarcoma Leukemia Giant Follicle Lymphosarcoma
3. Monocytic Acute—Subacute—Chronic	3. Reticulosarcoma Reticulum Cell Sarcoma Hodgkin's Disease (rapid, "Sarcoma") Reticulo-endothelioma Hodgkin's Disease (slow, "Granuloma") Mycosis Fungoides
4. Plasmacytic (Multiple myeloma)	4. Plasmacytoma (Solitary Myeloma)

In summary, they recommend selective therapy according to the rate of growth of the proliferative tissue as follows:

Acute leukemias (Lymphocytic, myelocytic)	Folic acid antagonist drugs are advised.
Acute monocytic leukemia	Nitrogen mustard. Treatment is further supplemented with antibiotics and transfusions.
Lymphosarcomas and the acute plasmacytic type. For the more chronic type.	Aminopterin. Extirpation and/or x-ray combined with nitrogen mustard.
Reticulosarcoma	X-ray and nitrogen mustard.
Hodgkin's Disease. When localized.	Extirpation and/or x-ray combined with nitrogen mustard.
If generalized.	Nitrogen mustard.

The authors have done a real service in preserving this excellent exhibit which covers so wide a field of investigation in the fundamental sciences, which has found specific clinical application. This monograph will be particularly useful for teaching of clinical hematology.

LANGUAGE FOR THE PRESCHOOL DEAF CHILD, Grace Harris Lassman, New York, Grune & Stratton, 1950, $5.50, 263 pp.

During the past few years technics for diagnosing auditory defects in young children have improved significantly. Educational treatment for the young deaf child can be begun earlier and effec-

tive methods to do this are delineated in this book. It should be helpful to parents in understanding goals to be set for the young child. The technics elaborated are those of language development rather than of simply speech, a much more fruitful concept. It is directed toward establishing communication and not at speech correction. The author points out that it is the child who sets the pace; she has an excellent understanding of the child's capacity to absorb new learning experiences. The book is well illustrated with charts and attractive pictorial material which add to its usefulness. The bibliography is excellent. It should be useful to those doing remedial work in the language area as well as to parents. The approach in general should be helpful to any child who has a significant delay in language development whether or not it is associated with hearing defect.

PATHOLOGIC PHYSIOLOGY: MECHANISMS OF DISEASE, edited by Wm. A. Sodeman, M.D., Philadelphia, W. B. Saunders Company, 1950, $11.50, 808 pp.

While this timely volume, written by 25 well qualified contributors, is addressed primarily to those concerned with the problems of internal medicine, its contents are naturally of great interest and practical value to all physicians who are interested in a rational explanation for the manifestations of disease. Emphasis on the mechanisms involved in producing the signs and symptoms of disease provides a clearer insight into its true nature and leads thereby to more effective methods of therapy.

As the editor indicates, the monograph does not aim to replace textbooks in physiology or clinical medicine but to supplement these and to help bridge the gap between them, so far as possible. It differs from textbooks on applied physiology largely in its special emphasis on clinical problems involving disturbed physiology. Nevertheless, its chapters contain a considerable mass of up-to-date basic physiologic information made more interesting to the physician by its being described in connection with clinical disorders with which he is already familiar.

The pediatrician will observe a lack of reference to, or allowance for, the unique character of some of his problems where the factors of growth and development impose special conditions. On the whole, however, the basic mechanisms described in the book are applicable to individuals of all ages, making it a valuable reference source for those who wish to familiarize themselves with the pathogenesis of a particular disease.